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Convenient Synthesis of β-Alkyl-Substituted Dihydrochalcones

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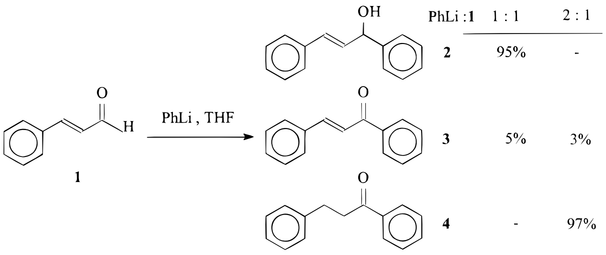
The chalcone system is the subject of renewed interest because it has been found to be a useful intermediate for the synthesis of compounds containing the benzopyran ring system and for other related substances.[1a] Several substituted chalcones have been found to exhibit pharmacological properties, and they seem to be involved in the biosynthesis of flavonoids.[1b] There is an ever-increasing concern about how the specific structure of organolithiums in solution,[2] and especially their degree of association,[3,4] affects the reactivity[2,5,6] and in many cases also the regio-[7,8] and stereochemistry[9] of their reactions. It was usually assumed by synthetic chemists that the "naked" carbanion (the monomer) was more reactive than higher oligomeric states;[10] nevertheless, different complexation effects could lead to a *decrease* in the reactivity of lower aggregates.[11]

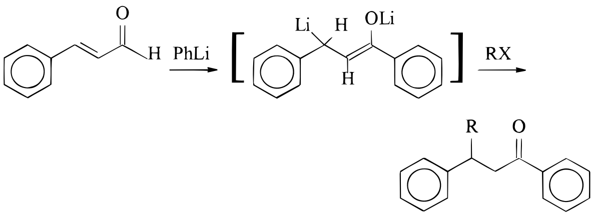
We have recently shown how the special aggregation features of lithium amides can be constructively used to lead their reactions toward the desired synthetic goal, in cases where different products can be obtained.[7] On other cases, the complex-induced proximity effects (CIPE) observed in some conveniently substituted substrates have been successfully used to promote remote directed lithiation, thus providing an expanded synthetic methology for β-substitution.[9,12] In this paper, the aggregation features of the organolithium reagent are conveniently used to promote addition of phenyllithium to (E)-cinnamyl aldehyde, **1**, β-lithiation, and subsequent electrophilic substitution, thus providing a convenient one-pot one-step methodology for the synthesis of a wide variety of β-alkyl-substituted dihydrochalcones.

A mechanistic study of the addition of phenyllithium to **1** has been recently reported.[13] This work showed that the reaction is highly sensitive to the reaction conditions; thus, in THF the (E)-1,3-diphenyl-2-propen-1-ol, **2**, is the main product, (yields >95%), and (E)-chalcone, **3**, and (E)-1,3-diphenyl-1-propanone, **4**, were found as traces. Nevertheless, by a careful choice of reaction conditions, the product distribution in the reaction mixture can be changed to give a high yield of **4**, the optimum conditions being [PhLi]:[**1**] = 2:1 and 7 h reaction time. Under these conditions, a brillant deep violet solution is formed and **4** is obtained in 97% yield (eq 1). The precursor of **4** is shown to be a β-lithiated intermediate, since treatment of the reaction mixture with D_2O gives **4** in 95% yield and 99% d_1. (When the isolated alcohol **2** was treated with PhLi, 79% of **4** and 21% of **3** were obtained.)



(1)

Addition of an electrophile to the reaction mixture and allowing the reaction to stand at 20 °C until decoloration of the solution is observed (2−8 h depending on RX) give the β-substituted dihydrochalcone (eq 2). A wide range of electrophiles have been assayed, and formation of the products is summarized in Table 1. Most of these electrophilic substitutions proceed in good yield, giving only one product, the corresponding dihydrochalcone (products **5**−**11**), in 77−100% yields. Table 1 shows that alkylation can be afforded with alkyl chlorides as well as with bromides; allyl bromide gave a very good yield of **11** (95%). Benzyl and hindered alkyl bromides, such as isopropyl and cyclohexyl, also gave good yields of the β-substituted dihydrochalcone.[14]



(2)

No detectable addition to the α-carbon was observed. Addition of alkyllithiums on the α-carbon of cinnamyl alcohol has received a great deal of interest in recent years,[15,16] and the reaction has been recently applied to the synthesis of asymmetric cinnamyl derivatives[17a] and chiral disubstituted cyclopropanes[17b] by running the reaction in the presence of

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[1] (a) Hepworth, J. D.; Gabbutt, C. D.; Heron, M. Pyrans and their Benzo Derivatives: Synthesis. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, Chapter 5. (b) Harborne, H. B., Ed. *The Flavonoids: Advances in Research since 1986*; Chapman and Hall: London, 1994.

[2] For pertinent reviews see: (a) Lambert, C.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1129−1140. (b) Nudelman, N. S. Carbonylation of Main-Group Organometal Compounds. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1989; Chapter 13 and references therein.

[3] Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573.

[4] Jedlicka, B.; Crabtree, R. H.; Siegbahn, P. E. M. *Organometallics* **1997**, *16*, 6021−6023.

[5] Kingsbury, C. L.; Smith, R. A. J. *J. Org. Chem.* **1997**, *62*, 4629−4634.

[6] Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514−1515.

[7] Nudelman, N. S.; Schulz, H. G.; García Liñares, G. E.; Bonatti, A. E.; Boche, G. *Organometallics* **1998**, *17*, 146.

[8] Nudelman, N. S.; Lewkowicz, E.; Furlong, J. J. P. *J. Org. Chem.* **1993**, *58*, 1847.

[9] Pippel, D. J.; Curtis, M. D.; Du, H.; Beak, P. *J. Org. Chem.* **1998**, *63*, 2−3.

[10] Williard, P. G. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 1 and references therein.

[11] Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448−454.

[12] Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 11391−11398.

[13] Nudelman, N. S.; Schulz, H. G.; García, G. V. *J. Phys. Org. Chem.* **1998**, in press.

[14] In a typical procedure, 3 mL of 1 M PhLi in anhyd THF was placed in a septum-capped round-bottomed reaction flask at 20 °C under a nitrogen atmosphere. Then 12 mL of THF and 132 mg (1 mmol) of (E)-cinnamaldehyde (freshly distilled) were added at once to the stirred solution. After 7 h, 1 mmol of the electrophile was added; the solution was allowed to stir until decoloration occurred and treated with 0.2 mL of methanol. The resulting dihydrochalcone was crystallized from methanol−water. The compounds were fully characterized by melting point, ^1H and ^{13}C NMR spectroscopy, and HRMS.

[15] Marumoto, S.; Kuwajima, I. *J. Am. Chem. Soc.* **1993**, *115*, 9021−9024 and references therein.

[16] Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152−161.

[17] (a) Klein, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853−8854. (b) Norsikian, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Org. Chem.* **1997**, *62*, 4898−4899.

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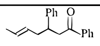
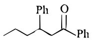
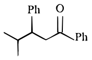
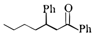
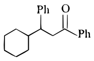
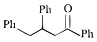
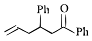
Table 1. Addition of PhLi to (*E*)-Cinnamaldehyde, 1, in THF at 20 °C. Reaction with Electrophiles, RX[a]

RX	Substituted dihydrochalcone		% Yields[b]
$CH_3CH{=}CHCH_2Cl$	**5**		77
n-PrBr	**6**		91
iso-PrBr	**7**		100
n-BuBr	**8**		83
c-C_6H_{11}Br	**9**		80
$PhCH_2Br$	**10**		81
$H_2C{=}CHCH_2Br$	**11**		95
n-BuCl	**8**		100
$PhCH_2Cl$	**10**		80

[a] $[PhLi]_0 = 0.21$ M and $[\mathbf{1}]_0 = 0.07$ M. [b] Determined by quantitative GC using Decalin as internal standard.

(−)-sparteine. In light of the different products obtained and the sensitivity to the reaction conditions, a different mechanism in which the dimer of the reagent is involved is suspected in the present case. In relatively dilute THF solution (260 mM), phenyllithium was established to be in a monomer−dimer equilibrium (39:61) by cryoscopy at −103 °C,[18] and this finding was corroborated by ^{13}C NMR (35:65).[19] Recent studies on the reactions of lithiated phenylacetonitrile with α,β-unsaturated carbonyl compounds show that aggregation effects strongly influences the 1,2- vs 1,4-regioselectivity in THF and in THF−binary solvent mixtures.[20]

In the present case, the reaction works well even with a ratio of [PhLi]:[**1**] = 2:1 with RX = $PhCH_2Br$, but in the other cases the best results and higher yields of β-alkyl-substituted dihydrocalcones were obtained with a ratio of [PhLi]:[**1**] = 3:1. Although additional experimental evidence is needed, theoretical calculations on the likely intermediates using dimeric PhLi gives a real transition state for the formation of the precursor of **4**.[21]

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Supporting Information Available: Experimental details for the preparation and reactions of **1**−**11**, characterization data for all new compounds **5**−**11**, and copies of their NMR spectra (11 pages).

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(18) Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972.

(19) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371−2379.

(20) Strzalko, T.; Seyden-Penne, J.; Wartski, L. *J. Org. Chem.* **1998**, *63*, 3295−3301.

(21) The transition state was searched and its geometry optimized by MNDO and PM3 methods. Calculations show that it is a real transition state, having only one negative vibrational frecuency corresponding to the reaction coordinate. Nudelman, N. S.; Schulz, H. G.; García, G. V. Submitted to *J. Chem. Soc., Perkin Trans. 2*, **1998**.