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Regioselective Metallation of Propylbenzene with Superbase: a Convenient Route to Stilbene Derivatives†

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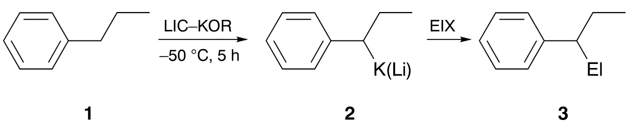
The benzylic metallation of propylbenzene has been elaborated with LIC–KOR superbase; the method has been applied in a new synthesis of stilbene derivatives.

Efficient methods have been published for the regioselective metallation of toluene[1] and ethylbenzene[2] with the superbasic LIC–KOR (butyllithium–potassium *tert*-butoxide) mixture.[3] The benzyl-type organometallics formed are stable enough (even at 60 °C in hexane[2]), thus their synthetic application does not require special conditions. In contrast, the benzylic metallation of propylbenzene has not been published. Previously, α-ethylbenzylalkali compounds were only prepared by the reductive cleavage of 1-methoxy-1-phenylpropane with alkali metals at low temperature[4] because these compounds underwent decomposition[4] when the temperature of the reaction mixture was higher than –20 °C. Trace amounts of α-ethylbenzyllithium formed in the reaction of propylbenzene with benzyllithium[5] (the equilibrium constant K is 1.1×10^{-4}).

We now report an efficient method for the benzylic metallation of propylbenzene and the application of this reaction in the synthesis of several stilbene derivatives. The target molecules have practical importance because of their anticancer activity.[6]

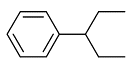
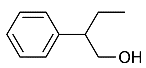
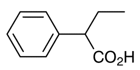
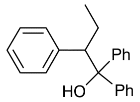
Detailed investigation of the reaction of propylbenzene (**1**) with LIC–KOR has shown that clean benzylic metallation can be achieved in neat tetrahydrofuran as well as in tetrahydrofuran–hexanes at –50 °C (Scheme 1). The organometallic product (**2**) was stable at –50 °C for several hours but it decomposed if the temperature rose above –20 °C (alkalihydride elimination followed by polymerization occurred within 2 h in neat hexane). However, addition of tertiary amine to the reaction mixture increases the thermal stability of **2**. Thus, the reaction could also be accomplished at 0 °C (5 h) in hexane in the presence of triethylamine.



Scheme 1

The efficiency and regioselectivity of the metallations were monitored by trapping **2** with different electrophiles (Table 1). All of the products were isolated and characterized by their physical constants and spectra, which were identical with those of authentic samples known from the literature. Though the hydroxymethyl derivative **3b** was prepared with low efficiency, the ethyl (**3a**) and the carboxylic acid (**3c**) derivatives as well as the benzophenone adduct (**3d**) were obtained with satisfactory to good yields.

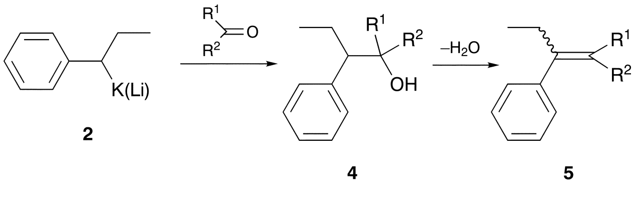
Table 1 Reaction of **2** with different electrophiles

ElX	Product	Yield (%)	Ref.
Et	 **3a**	39	8
CH_2O	 **3b**	20	9
CO_2	 **3c**	48	10
Ph_2CO	 **3d**	68	11

We observed that water elimination from **3d** partially occurred during the acidic work-up and purification procedure on silica gel. Therefore, we used the crude addition products (**4**, Scheme 2) for the preparation of stilbene derivatives (**5**). The elimination reaction was practically quantitative when it was accomplished in a boiling ethanol–hydrochloric acid mixture. The pure products were isolated as a *Z*/*E* mixture by column chromatography (Table 2). In the case of **4a** ($R^1 = H$, $R^2 =$ phenyl) a *ca.* 1:1 mixture of the *erythro* and *threo* isomers was formed. The water elimination resulted in a 1:1 mixture of the *Z*- and *E*-stilbenes (**5a**) together with some isomer product (1,2-diphenylbut-2-ene, *Z*:*E* = 2:1.5).

The overall yield of the reaction sequence (metallation, addition, elimination) was excellent when the benzophenone-type oxo compound contained a fluoro or dimethylaminoethoxy substituent in the *para* position. (1-Phenylpropylmagnesium chloride failed to react with the benzophenone bearing a dimethylaminoethoxy side chain in the *para* position.)

Consequently, our new method for the clean, benzylic metallation of propylbenzene is a synthetically useful route to α-ethylbenzylpotassium, which can serve as a key intermediate of an efficient and convenient synthesis of



Scheme 2

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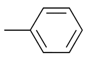
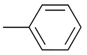
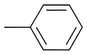
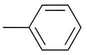
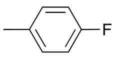
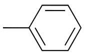
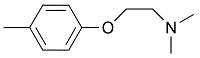
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 2 Preparation of (*Z*)/(*E*)-stilbene derivatives

R^1	R^2	Product	Yield (%) (*Z*/*E*)	Ref.
H		**5a**	66 (1:1)[a]	12, 15
		**5b**	84	11, 13
		**5c**	89 (1:1)	14
		**5d**	85 (1:1)	7

[a] The crude product contained 1,2-diphenylbut-2-ene (20%).

(*Z*/*E*)-stilbene derivatives such as **5d** (Tamoxifen,[7] a drug against mammary cancer).

Experimental

Starting materials were purchased from Fluka AG. Butyllithium solution was delivered by Chemetall GmbH, Frankfurt. All commercial reagents were used without further purification. Air- and moisture-sensitive materials were stored and handled in Schlenk tubes or Schlenk burettes under dry, pure nitrogen. Tetrahydrofuran was dried by distillation after the characteristic blue colour of the *in situ* generated sodium diphenylketyl was found to persist.

Metallation and Derivatization of Propylbenzene (*General Procedure*).—Potassium *tert*-butoxide (1.3 g, 12 mmol) was added to a precooled (–50 °C) mixture of dry tetrahydrofuran (15 ml), propylbenzene (1.7 ml, 1.4 g, 12 mmol) and a 1.5 M solution of butyllithium (8.4 ml, 13 mmol) in hexane. The reaction mixture was stirred at –50 °C for 5 h. The corresponding electrophile reagent (10 mmol, Table 1) was added before the cooling bath was removed. Water (15 ml) was poured into the mixture at 20 °C; the phases produced were then separated and the crude products were isolated from the organic solutions by standard methods, except for compound **3c** which was obtained from the aqueous phase by acidification.

Preparation of 1,1,2-*Triphenylpropene* (*Typical Example*).—The crude oily product of **3d** obtained by the above described procedure (using benzophenone as electrophile) was dissolved in a mixture of EtOH (17 ml) and 10 M solution of HCl in H_2O (2.5 ml). The solution was boiled under reflux for 2 h then concentrated *in vacuo*. The residue was purified by column chromatography (Kieselgel, eluent hexane) to yield pure product (**5b**, Table 2).

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