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2,4,6-TRI-t-BUTYLPHENYLLITHIUM AS A BASE-----KINETIC DEPROTONATION OF BENZYL METHYL KETONE

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Abstract: An extremely bulky lithium reagent, 2,4,6-tri-t-butylphenyllithium, was applied for deprotonation of benzyl methyl ketone to give the kinetic enol ether by "in situ" quenching with chlorotrimethylsilane as the major product indicating that the reagent serves as a hindered base.

Sterically hindered compounds have been of interest in view of their protecting nature of reactive sites or molecules. We have been successful in preparation and characterization of unusual phosphorus compounds in low coordination state by introducing an extremely bulky organic moiety, 2,4,6-tri-t-butylphenyl group. We have employed the corresponding lithium reagent as a nucleophile to prepare such compounds as diphosphenes,1) phosphaethylenes,2) 1-phospha-allene,3) and 1,3-diphospha-allene.4)

Very recently, Oehme and Weiss reported the properties of 2,4,6-tri-t-butylphenyllithium toward silanes5) as a base rather than a nucleophile. We now wish to report some interesting reactions toward organic ketones in which 2,4,6-tri-t-butylphenyllithium serves as a base.

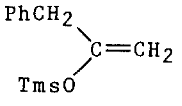
Enolates are very important reagents for organic synthesis and have long been used for C-C coupling reactions as represented by aldol condensation.6) Silyl enol ethers are also useful for such purposes.7)

"In situ" quenching has often been used not only to utilize a reactive intermediate for organic synthesis but also to determine such species during the reaction. Krizan and Martin were successful in trapping ortho-lithiated cyanobenzenes.8) On the other hand, Corey and Gross9) were able to obtain selective and kinetically controlled enol ethers by using chlorotrimethylsilane as an "in situ" trapping reagent. They obtained, for example, a 1:1 mixture of non-conjugated (2) and conjugated (3 and/or 4) silyl enol ethers as the reaction products from benzyl methyl ketone (1) and chlorotrimethylsilane, using lithium diisopropylamide as a base and tetrahydrofuran (THF) as a solvent at -78 °C, while the conventional two-step procedure gave only the conjugated enol ether(s) (3 and/or 4) as a thermodynamically quenched product.7)

Alkyllithium compounds are basic, in general, but normally they are used to accomplish C-C bond formation reactions. If, however, the alkyl group is sterically bulky, the lithium compound might behave as a base rather than a nucleophile. In fact, Seebach et al.[10)] suggested that mesityllithium can be used to generate kinetic enolates. Utilization of such alkyllithium as a base might have the advantages over amide reagents such as lithium diisopropylamide as follows. (1) Alkyllithium is a strong base rather than a nucleophile. (2) An alkane is formed after abstracting proton, which does not interfere the reaction, while an amine formed from an alkali-metal amide is potentially an electrophile. (3) If the alkyl group is sterically bulky, the reaction might proceed in a regio-selective fashion. (4) The alkane formed is easily removed from the reaction mixture. Furthermore, hindered bases are valuable reagents for organic synthesis and their increasing use is evident in recent literature.[11)]

Benzyl methyl ketone (**1**) is among the severest substrates to be checked for the formation of kinetic enolates, because the benzylic protons are much more acidic (pK_a 15.91) than the methyl protons (pK_a 18.27), which are less crowded.[12)] Therefore a bulky base could abstract a proton from methyl group rather than more acidic protons of benzyl. We employed "in situ" quenching to determine the selectivity of 2,4,6-tri-t-butylphenyllithium toward ketone **1**. The typical present procedure is shown in the following scheme. 2,4,6-Tri-t-butylphenyllithium was prepared from the corresponding bromobenzene and butyllithium in THF at -78 °C[1)] and was cooled or warmed to the prescribed temperature. Into the lithium reagent at that temperature were added chlorotrimethylsilane and the ketone **1** successively and the reaction mixture was stirred for 30 min. Triethylamine was then added and the mixture was warmed up to room temperature followed by the usual workup.

$$\underset{1.2\ \text{equiv.}}{\text{Base}}\ /\ \underset{3\ \text{ml}}{\text{THF}}\ \xrightarrow[2.0\ \text{equiv.}]{\text{TmsCl}}\ \xrightarrow[1.0\ \text{mmol}]{PhCH_2C(O)CH_3\ (\mathbf{1})}\ \xrightarrow[2.3\ \text{equiv.}]{Et_3N}\ \xrightarrow{\text{aq. } NaHCO_3}$$



(**2**)

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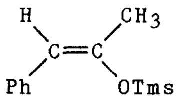

(**3**)

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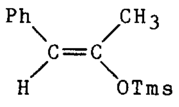

(**4**)

The table shows some results on the reaction products from the ketone **1** by the "in situ" quenching method with various bases as listed. The results indicate that 2,4,6-tri-t-butylphenyllithium is the best base to obtain kinetically controlled silyl enol ether from **1**, compared with other bases, probably due to the steric bulkiness of 2,4,6-tri-t-butylphenyl group. It is interesting to note that the temperature dependence to the selectivity is observed, but

TABLE Formation of Silyl Enol Ethers from Benzyl Methyl Ketone (**1**)

Base[a]	Temp. /°C	Yield of (**2**+**3**+**4**)/%	Composition[b] **2**	: **3**	: **4**
ArLi	-97	91	59	29	12
	-78	89	69	16	15
	-50	87	74	9	17
	-25	90	74	8	18
	0	81[c]	69	12	19
MesLi	-78	89	32	10	58
	-50	90	32	9	59
	-25	40[d]	8	75	17
$(i\text{-}Pr)_2NLi$	-78	98	31	5	64
	-50	98	30	5	65
	0	97	29	23	48
$(c\text{-}Hex)_2NLi$	-78	98	41	6	53
	-50	94	40	6	54
TmpLi	-50	94	34	7	59
Tms_2NLi	-50	99	10	6	84
	-25	91[e]	13	15	72

a) Ar=2,4,6-tri-t-butylphenyl; Mes=mesityl; c-Hex=cyclohexyl; Tmp=2,2,6,6-tetramethylpiperidyl; Tms=trimethylsilyl. b) The product ratio was determined by VPC analysis (OV-1). c) 7% of **1** was recovered. d) **1** (60%) was recovered and MesTms was formed. e) Tms_3N was formed along with ~10% recovery of **1**.

the reason is not clear yet why the reaction conditions around -50 °C gave the best results to give **2**. At higher temperatures the "in situ" quenching reaction gave by-products which were assigned to be nucleophilic adducts of lithium compounds and the silyl chloride, causing low yields of silyl enol ethers, while 2,4,6-tri-t-butylphenyllithium did not give any traces of the corresponding silane.13) House et al. reported7) that the ratio of E and Z of the thermodynamic conjugated products from the two-step procedure were variable depending upon the reaction conditions employed (**3** : **4** = 96:4 ~ 14:86, i.e., base, solvent, reaction time, etc.), while Corey did not mention9) the ratio of formation of E and Z isomers of conjugated enol ethers. Under our reaction conditions in the presence of triethylamine, the product ratio of **2**, **3**, and **4** was reproducible. Thus, 2,4,6-tri-t-butylphenyllithium might be very useful as a new hindered base for organic synthesis. Further studies on this subject is now in process.14)

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13) 2,4,6-Tri-t-butylphenyllithium appears unstable at higher temperature since the reagent abstract proton from THF to give 1,3,5-tri-t-butylbenzene, which was confirmed by a separate experiment using THF-d_8.
14) Preliminary results indicate that both acetone and acetophenone afford aldol type of adducts with benzaldehyde using 2,4,6-tri-t-butylphenyllithium as a base: T. Nakamura, Y. J. Choi, M. Yoshifuji, and N. Inamoto, presented at the 52nd National Meeting of the Chemical Society of Japan, Abstr. 2L42, Kyoto, April 1986.

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