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Regioselective Alkylation of Lithium Enolates Derived from 2-Heptanone

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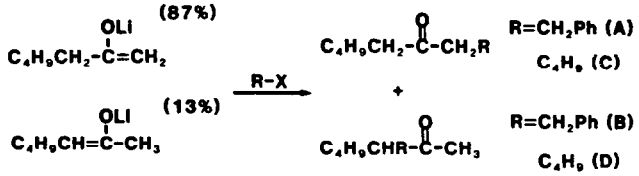
Abstract: The benzylation and n-butylation of the kinetic enolate mixture derived from 2-heptanone has been studied in DME in the absence and in the presence of lithium ion complexing agents (triglyme, benzo-14-crown-4, DMF (neat), DMF, and HMPA).

The regioselective formation of enolates derived from unsymmetrical ketones and their subsequent alkylation have been the subject of extensive research. Whereas numerous effective and ingenious methods have been reported for the regioselective formation of the anion, the alkylation step has frequently encountered serious difficulties. Equilibration of enolates accompanying the alkylation process has resulted in loss of regioselectivity and in the formation of polyalkylated products.[1,2,3] An especially notorious example of this phenomenon is encountered in the benzylation of the kinetic lithium enolate mixture derived from 2-heptanone[4] (Reaction 1).



In spite of the fact that the mixture consisted of 87% terminal and 13% internal enolates, benzylation in DME under a variety of conditions with respect to time of reaction and concentration of reactants resulted in poor regioselectivity. In addition, substantial polybenzylation accompanied rather poor overall yields of monobenzylated products. Indeed, in a preparative run a 41% isolated yield of primarily the internal benzylated product was reported. These results have been attributed to the existence of complex ion aggregates in solution resulting in a slow rate of alkylation compared to the rate of equilibration of enolates. It seemed reasonable to assume that if the kinetic enolate mixture could be substantially activated toward alkylation, then proton transfer and the resulting equilibration and polyalkylation might not be an effective competing processes in the presence of excess alkylating agent. This Communication reports the use of a variety of Li^+ complexing agents to accomplish these ends.

Successful regioselective benzylation of the kinetic mixture of enolates derived from 2-heptanone has been accomplished. The results are reported in Table 1. Clearly, all ligands reported in this study produce more terminal than internal alkylation; the effectiveness is in the order HMPA (4.9 equiv.) > DMF (neat) > benzo-14-crown-4 (1.61 equiv.) > DMF (6.18 equiv.) > triglyme (1.94 equiv.). In fact, HMPA was found to produce a ratio of terminal to internal benzylation of 11/1 with an absolute yield of terminal benzylation product of 77%- a percent quite close to the absolute amount of terminal enolate initially present. In all cases, only trace amounts of O-alkylated products were observed. In a

Table 1. Benzylation of Enolates Derived from 2-Heptanone in the Presence of Li^+ Complexing Additives (a,b,c)

	Complexing Agent	% Yield A	% Yield B	% Yield Dibenzylation	Ratio A/B
1.	None	26	39	21	0.67
2.	Triglyme (1.94 equiv)	30	17	31	1.8
3.	Benzo-14-crown-4 (1.61 equiv)	45	10	34	4.5
4.	DMF (6.18 equiv)	36	12	14	3
5.	DMF (neat)	65	11	21	6
6.	HMPA (4.9 equiv)	77	7	17	11

(a) Into a 25 mL, 3-necked flask equipped with a stir bar, thermometer, and septums were added a small amount of a,a-bipyridyl and 2.2 mmole of ethereal methyllithium. The ether was evaporated in vacuo and the methyllithium redissolved in 4.0 mL of DME. A solution of silyl enol ether mixture (87% terminal-13% internal) of 2-heptanone (2.0 mmole) and a weighed amount of cyclododecane internal standard in 4.0 mL of DME was added and the resulting solution stirred at room temperature for 1 hour. At this time a solution of the appropriate ligand in 2.0 mL of DME was added and allowed to stir for 10 minutes. Benzyl bromide (10 mmole) was then added rapidly via syringe. Aliquots were withdrawn at 1, 3, 5, 10 and 30 minutes, quenched in cold, saturated, aqueous $NaHCO_3$ and extracted with ether. The ether layers were washed once with water and analyzed by GLC on a 25% SE-52 on Chromosorb W column. (b) The % yields reported are those after 30 minutes of reaction time. (c) The reaction performed in pure DMF was carried out in a similar manner except that after the generation of the enolate anion, the DME was removed in vacuo and replaced by the same volume of DMF.

Table 2. n-Butylation of Enolates Derived from 2-Heptanone in the Presence of HMPA (a)

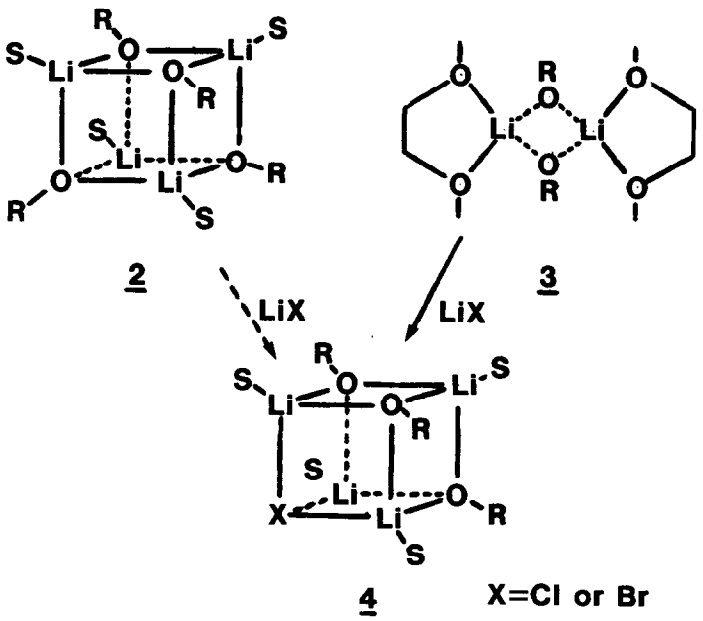
	HMPA (mmole)	Silyl Ether (mmole)	n-BuI (mmole)	DME (mL)	Rxn Time	% Yield C	% Yield D
1.	None	4.17	20	16	1 min	2	0.3
					10 min	8	2
					3 hr	8	21
2.	21	4.20	20	20	1 min	30	18
					5 min	30	23
					6 hr	26	21
3.	10	1.98	20	20	1 min	44	14
					2 hr	36	24
4.	5	0.98	10	10	15 sec	16	3

(a) Into a 50 mL, 3-necked flask equipped with a stir bar and septums was added 4.4 mmole of ethereal methyllithium. The ether was evaporated in vacuo and replaced by 10 mL. of DME. A solution of silyl enol ether mixture (87% terminal-13% internal) of 2-heptanone (4.20 mmole) and tetradecane internal standard (0.728 mmole) in 6.0 mL of DME was added at room temperature and allowed to stir for one hour. A solution of HMPA (3.78 g, 21 mmole) in 4.0 mL of DME was then added and allowed to sir for 10 minutes. At this time 2.4 mL (20 mmole) of n-butyl iodide was rapidly added via syringe. Aliquots were taken at various time intervals, quenched with 1M NH_4Cl and extracted with ether. The ether layers were washed once with water and analyzed by GLC in the same manner as the benzylation reaction.

preparative scale run using HMPA, a 60% absolute yield of benzylated products was obtained in which 85% was the terminal isomer. It is interesting to note that the rates of reaction in the presence of all the ligands in Table 1 are much more rapid than in their absence. For instance, in the presence of benzo-14-crown-4, DME or HMPA, the reactions were complete in less than one minute. Indeed, when benzo-14-crown-4 was used as the complexing agent, the solid LiBr-crown complex[5] precipitated from the reaction mixture almost immediately after the addition of benzyl bromide.

Since benzyl bromide is considered to be a reactive electrophile, the regiochemistry accompanying the use of the less reactive alkylating reagent, n-butyl iodide, was also investigated. Table 2 summarizes the results in DME in the absence and in the presence of HMPA (5 equiv.). Several concentrations of the kinetic enolate mixture were studied as a function of time. In the absence of complexing agent, at least eight "major" products were obtained along with many minor components. In addition, the reaction proceeded at a very slow rate. In the presence of HMPA, however, not only was the rate accelerated but the product mixture showed a definite preference for the terminal n-butylated product. Comparison of Run 2 with Runs 3 and 4 indicate that as the concentration of the enolate mixture decreases, the initial ratio of terminal to internal n-butylation product increases. In a preparative scale run using HMPA (with 0.1 M enolate) a 40 % absolute yield of mono-n-butylated products was obtained in which 56 % was the terminal isomer. Thus, even with the poorer electrophile, the presence of a Li^+ complexing agent results in greater regioselectivity.

Jackman et. al.[2,6-9] have presented NMR (^1H, ^{13}C, ^7Li) evidence indicating that lithioisobutyrophenone (1) exists as tetramer 2 in dioxolane, dioxane, and tetrahydrofuran, as primarily dimer 3 (80% dimer, 20% tetramer) in DME, and as aggregate 4 in the presence of LiCl and LiBr.



2 3 4

Jackman has also noted that, although 15-crown-5 and 12-crown-4 do not produce an observable change in the ^{13}C NMR spectrum of 1 in either dioxolane or DME, the rates of alkylation were accelerated. In contrast to this, HMPA causes substantial shifts in the ^{13}C NMR spectrum as well as increased rates of alkylation. Jackman concluded that the crowns and HMPA produce new species which are more reactive than 2 or 3. The nature of the new species formed in the presence of the crowns was never discussed. It has already been mentioned that in the benzylation and n-butylation of the kinetic enolate mixture derived from 2-heptanone in DME, a marked increase in rate was observed in the presence of all the ligands reported in this communication- observations consistent with those of Jackman. While it is not difficult to rationalize the rate enhancement in the presence of HMPA based upon the ^{13}C NMR results of Jackman, the corresponding rate enhancements in the presence of the polyether complexing agents are somewhat more difficult to understand. Since it has been independently observed that both the triglyme and the benzo-14-crown-4 form strong complexes with LiBr in DME[5], the following hypothesis is suggested. In the absence of added complexing agent, the initial stages of reaction take place on dimer 3. As the reaction progresses, the LiBr which is formed transforms the remaining enolate to aggregate 4. If it is assumed that 4 is less reactive than 3, then the rate of alkylation should become slower. It is conjectured, therefore, that in the presence of the polyether complexing agents, LiBr is made "less available" for effectively aggregating with the lithium enolate thereby allowing the more reactive dimer to persist. Thus, the Li^+ complexing agents may be species which diminish deactivation instead of promoting activation of the dimer in the solvent DME.

In conclusion, experimental results related to the benzylation and n-butylation of a kinetic enolate mixture derived from 2-heptanone in the absence and presence of a variety of Li^+ ligands has been presented. In addition, a hypothesis has been suggested to rationalize the increased rates of reaction in the presence of polyether ligands.

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