

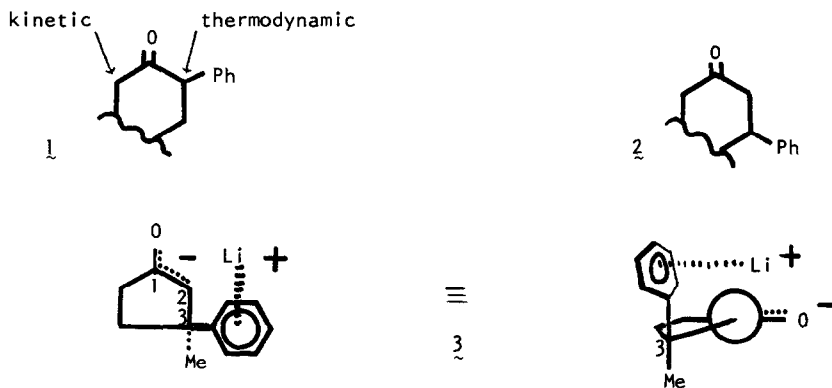
A SURPRISING EFFECT OF 3-ARYL GROUPS ON THE REGIOCHEMISTRY OF FORMATION OF CYCLOPENTANONE LITHIUM ENOLATES. EVIDENCE FOR LITHIUM-ARENE π -COORDINATION

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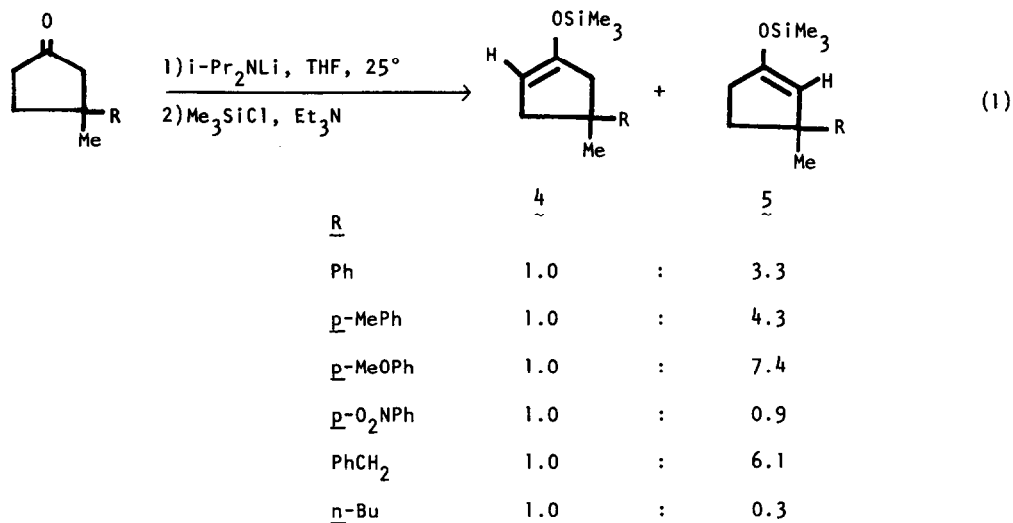
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(Received in USA 31 May 1977; received in UK for publication 18 July 1977)

Regiospecific generation of one enolate structural isomer of an unsymmetrical ketone is often a very important operation in organic chemistry¹. When the unsymmetrical ketone bears an adjacent substituent such as an aryl group, which can stabilize an incipient enolate ion, then that thermodynamic enolate is produced under equilibrating conditions. When the other (*i.e.*, kinetic) enolate is desired, proton abstraction by a non-nucleophilic hindered base under non-equilibrating conditions is routinely used (*e.g.* **1**)^{1,2}. If the substituent aryl group is located on a β -carbon atom (*e.g.* **2**)³, then resonance stabilization of an incipient enolate ion is no longer important and inductive stabilization may play a role (*e.g.* PhCH₂CO₂H is a slightly stronger acid than PhCH₂CH₂CO₂H)⁴. The magnitude of such inductive stabilization should be directly related to the electron-withdrawing ability of *p*-substituted phenyl groups: *p*-nitrophenyl > phenyl > *p*-methoxyphenyl. We now report the surprising observation that 3-arylcyclopentanones in the presence of lithium diisopropylamide at room temperature enolize preferentially toward the 3-aryl group and that this regiochemical preference is greater for 3-anisylcyclopentanones than for 3-*p*-nitrophenylcyclopentanones. Based on this finding and on the effect of coordinating solvents on the regiochemistry of enolate formation, we postulate a critical lithium-arene π -coordination represented tentatively as in structure **3**.



We have allowed a series of 3-methyl-3-arylcyclopentanones to react under nitrogen with 1.0 equiv of lithium diisopropylamide in tetrahydrofuran (THF) at 25° for 1 hr, after which a mixture of trimethylsilyl chloride and triethylamine was added⁵; glpc analysis, isolation (>70% yields) and identification of enol silyl ethers 4 and 5 led to the results shown in eq. 1. Enol silyl ethers 4 show a characteristic nmr vinylic H multiplet centered at $\delta 4.64$ ⁵, whereas enol silyl ethers 5 show a typical vinylic H triplet ($J \approx 1\text{Hz}$) centered at $\delta 4.82$.



The directing effect of a p-methoxyphenyl group is larger than that of a p-methylphenyl group which is larger than that of phenyl itself; a p-nitrophenyl substituent is the least directing aryl substituent examined. This ability of a remote aryl group to direct the regiochemistry of enolate formation parallels the π -electron-donating ability of the aromatic group⁶. A 3-benzyl substituent, which cannot reasonably stabilize the enolate corresponding to enol ether 5 by inductive forces, directs enolate formation even more effectively than a 3-phenyl group. And finally, 3-methyl-3-n-butylcyclopentanone (which lacks any 3-aryl substituent) reacted under these conditions to give predominantly the expected enol ether 4.

If a lithium-arene π -coordination is indeed responsible for this unusual regiochemistry of enolate formation as depicted for example in structure **3**, then the magnitude of this effect should be inversely related to the coordinating ability (e.g. DME>THF>Et₂O) of the solvent used⁷. Indeed this is the case; 3-methyl-3-phenylcyclopentanone reacted under these conditions to give enol silyl ethers **4** and **5** in the following ratios - 1.0:1.8 (DME), 1.0:3.3 (THF), and 1.0:5.0 (Et₂O).

Control experiments established (1) that enol silyl ethers **4** and **5** were both stable to the reaction conditions and (2) that the lithium enolate precursors to silyl ethers **4** and **5** equilibrated under the reaction conditions. For example, performing eq. 1 in THF at 0° led to ethers **4** and **5** in a 1.0-1.8 ratio, whereas repeating this experiment with the cycle 0°→25°→0° led to **4** and **5** in a ratio of 1.0:3.3, characteristic of the original 25° experiment. Furthermore, performing eq. 1 at -78° in the absence and in the presence of hexamethylphosphoramide gave **4** and **5** in ratios of 1.0:0.7 and 1.0:3.3, respectively. We have found that the enolate precursors to enol silyl ethers **4** and **5** react with trimethylsilyl chloride at the same rate⁸, and that similar but less dramatic effects are present in the corresponding 3-arylcyclohexanones.

No apparent literature precedent exists for such a lithium- π -electron interaction which directs the regiochemistry of enolate formation as we have described here. Lithium ion coordination with the π -electrons of unsaturated organic groups, however, does have precedent. For example, an x-ray study of benzyllithium revealed lithium ion coordination to the π -cloud of the benzyl group⁹, and 3-butenyllithium has been shown to have some lithium- π -electron interactions which were claimed to be important in directing the stereochemistry of alkyllithium initiated polymerization of butadienes¹⁰. Our study of the stereochemistry of alkylation of 3-arylcyclopentanone enolates is reported in the accompanying paper¹¹. Finally, to the extent that the lithium atom in lithium enolates resembles the hydroxyl hydrogen atom in enols and alcohols, the documented hydrogen-arene π -coordination in 0-arylphenols¹² and in 2-phenylethanol¹³ may be relevant.

We believe that the results reported here have broad implications generally for the chemistry of lithium-containing unsaturated organic compounds and specifically for formation and reaction of other unsaturated lithium enolates and lithium enamides¹⁴. We are studying various spectra of our enolate intermediates as well as the effect of changing the positive counterion.

Acknowledgment. We thank the National Science Foundation (GP-33667 and GP-43419X) for generous support.

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