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The Stereochemistry of Enolate Formation in THF-Hexane Mixtures

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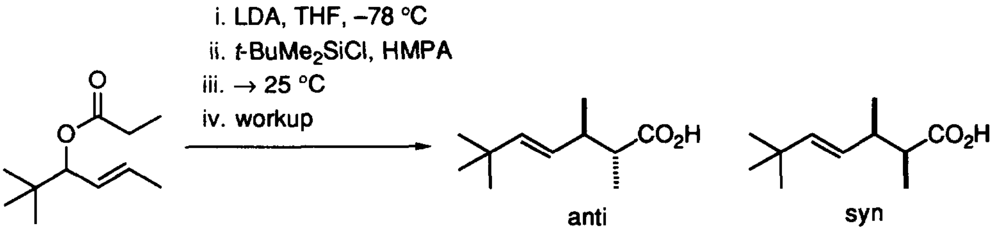
Abstract: The effect of solvent on the stereochemistry of deprotonation of 4-heptanone in THF-hexane mixtures is plotted in the figure on the following page. The *E/Z* ratio varies from 1.5 in pure THF to 0.7 in 90% hexane.

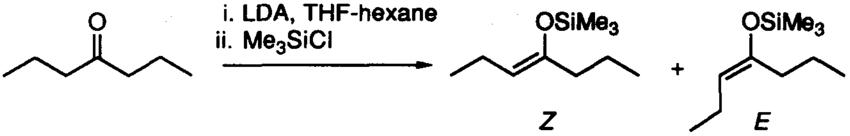
In connection with a synthetic project, we had occasion to repeat an Ireland enolate-Claisen rearrangement that had been carried out earlier in these laboratories:[1]



(1)

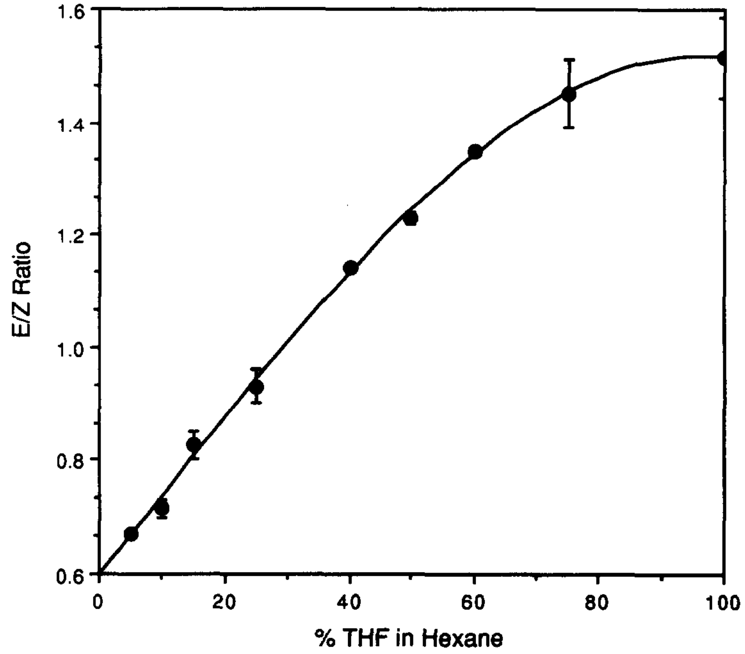
To our surprise, we were unable to reproduce the stereoselectivity that had been observed previously. A careful evaluation of all of the reaction variables revealed one significant difference. In the earlier work, the LDA had been prepared by the reaction of diisopropylamine with 1.5 M *n*-butyllithium in hexane, whereas we had used 2.5 M *n*-butyllithium in hexane for the later work. Since, as is customary, the hexane had not been removed, the two reactions had been carried out in different media–6:1 THF/hexane in the former case and 3:1 THF/hexane in the later case.

Because of this experience, we decided to carry out a brief investigation of the quantitative effect of THF-hexane composition on the stereochemistry of enolate formation. The ketone we employed for this study was 4-heptanone (eq 2). Enolate compositions were evaluated by trapping with trimethylsilyl chloride and analyzing the resulting silyl enol ethers by ^{1}H NMR spectroscopy. All deprotonations were carried out in triplicate.



(2)

The data, which are plotted below, show that the amount of hexane in the solvent is an important variable; in pure THF the *E/Z* ratio is 1.5 whereas in 90% hexane it is 0.7. Similar results were obtained with 3-pentanone. For these ketones, there is little difference between pure THF and 30% hexane, which is the range that covers most of the literature deprotonation reactions. Although this justifies the traditional practice of ignoring the amount of hexane that is introduced with the *n*-butyllithium the results are mechanistically interesting. The observed trend is somewhat counterintuitive, since the more polar medium (pure THF) gives higher *E* selectivity, a trend that seems inconsistent with the well-known Ireland deprotonation model.[2] That is, one might have expected that a less polar medium would lead to a tighter deprotonation transition stucture, resulting in a higher fraction of *E* enolate. Instead, just the opposite is observed. The reason for this unexpected result is unclear, but it may reflect different states of aggregation of the active base as the solvent polarity is changed.



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References and Notes

1. Radel, P. A. *Ph. D. Dissertation*, University of California, Berkeley, 1986.

2. Ireland, R. E.; Muller, R. H.; Eillard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

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