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# HIGHLY STEREOSELECTIVE FORMATION OF ENOL SILYL ETHERS

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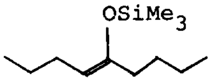
While regiochemical aspects of enolate chemistry have been studied extensively,[1] virtually no attention has been paid until recently to geometry of the double bond of enolate anions. Correlation of this geometry with stereochemistry of aldol reaction[2] is one of the early examples which received attention,[3] and very recently geometrically homogeneous enolates have proved to provide some solutions to control of stereochemistry in acyclic systems.[4.5] There remain , however, many problems to be unveiled[6] with respect to the effects of the enolate geometry.[7] One serious factor that has prevented the investigation is, unquestionably, difficulties at the starting point, the stereo-controlled enolate formation.[8] This communication discusses solutions to this synthetic problem.

A recent paper from our laboratory reported a silylating reagent, alkyl trimethylsilylacetate,[9] based on a new methodology of enolate generation.[10] In order to explore further the potential of this new reagent, we examined the reaction with acyclic ketones. Thus, 5-nonanone was treated with 1.2 equiv of ethyl trimethylsilylacetate (ETSA) at 0 °C in the presence of 1 mol% of tetrabutylammonium fluoride (TBAF). Surprisingly, we observed exclusive formation of Z-enol silyl ether 1 (91% distilled yield). The isomeric purity was established, in comparison with the NMR spectrum of an authentic E-Z mixture,[5] by the absence of a sharp triplet associated with the E isomer.[11] The assignment was also in accordance with the general rule of the NMR spectra of enol silyl ethers.[6b,12] Silylation of 3-pentanone at -78 °C proceeded also highly stereoselectively, giving (Z)-3-trimethylsiloxy-2-pentene 2 of 99.5% isomeric purity[13] ( quantitative yield by GLC, 78% distilled yield). The isomeric purity was determined by GLC (QF-1 or XE-60) in comparison with an authentic E-[5] or Z-enriched[6b] mixture, and also by NMR analysis.[12,14]



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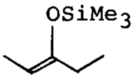

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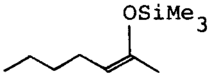

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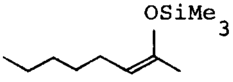

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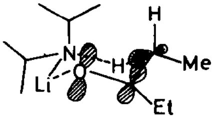
We also noted excellent stereoselectivity with unsymmetrical ketones. Treatment of 2-heptanone with 1.2 equiv of ETSA in THF at -78°C for 5 min, then at 20°C for 24 hr afforded 3[6b] in 55% yield together with the regioisomer in 9% yield.[13] Similarly, silylation of 2-octanone gave 4 and the regioisomer (86:14) in 91% distilled yield. In both cases, none of the geometrical isomers of 3 or 4 were formed; the clearly distinguishable sharp triplets of the stereoisomers[6b] were not detected at all.

Since enol silyl ethers could be transformed into the corresponding lithium enolate with retention of the stereochemistry,[6b] the present reaction conprizes a method for the preparation of stereo-homogeneous Z-enolate anions.

Having established the procedure for generation of Z-enolate anions, we then seeked to generate E-enolates. The best current preparation of E-enriched enolate anions involves the deprotonation with lithium diisopropylamide in THF at -78°C;[5,6b] when applied to 3-pentanone, the E-selectivity was 77%.[5] A six-center transition state 5 has been considered to determine the selectivity.[5] If the steric repulsion associated with the axial isopropyl group in 5 is the sole controlling factor, substitution of the isopropyl with a tertiary alkyl group would enhance the E-selectivity. In fact, lithiation of 3-pentanone with lithium 2,2,6,6-tetramethylpiperidide (LiTMP)[15] in THF followed by quenching with chlorotrimethylsilane quantitatively gave 6 in 84% isomeric purity.[13] The observed selectivity with LiTMP seems to indicate that the formation of the Z-isomer with lithium amide bases does not simply stem from the insufficient steric bulk of the secondary amine moiety.



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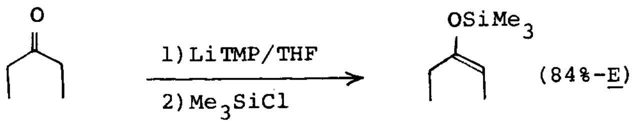

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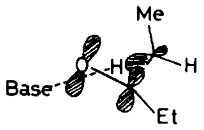
In order to gain insight about the *Z*-selection in the reaction of alkyl trimethylsilylacetate, 3-pentanone was subjected to the silylation with ETSA under various conditions. In the first run, the reaction was carried out at 0 °C in the presence of TBAF to exhibit 97% *Z*-selectivity.[13] The reaction catalyzed by KCN-18-crown-6 at 0 °C[16] also met with the decrease in the selectivity. Ireland reported 95% *Z*-selectivity on lithiation with LDA in THF-HMPA.[5] Since TBAF smoothly equilibrates enol silyl ethers in a regiochemical sense,[9,17] we suspected that it is also effective for equilibration of the stereochemistry. In fact, when 99.5% pure *2* was treated with 3 mol % of TBAF for 24 hr at 20 °C in THF, a 13:87 *E*-*Z* mixture formed.[13] Treatment of 21:79 mixture, prepared by $Me_3SiCl/Et_3N$,[6b] under the same conditions in ethyl acetate resulted in 24:76.[13] The equilibrium *E*-*Z* ratio of the enol silyl ether of 5-nonanone was determined to be 28--29:72--71[13] by treatment of pure *1* or a 49:51 mixture of *1* and the *E*-isomer with TBAF as described above.

The ready isomerization of enol silyl ethers indicates, in turn, that the excellent *Z*-selectivity with alkyl trimethylsilylacetate has originated from kinetic selection.[17] The contrasting behavior of ETSA-TBAF and LDA or LiTMP in THF evidently depends on the nature of the countercation of the base.[5] In view of the neutral nature of the ammonium cation in the former case, the stereochemistry must have been determined in the transition state *7* instead of *5* by the steric repulsion between two alkyl chains.



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The excellent *Z*-selection with alkyl trimethylsilylacetate together with the fair *E*-selectivity of LiTMP reported here will provide a basis for synthetic utilization of the geometry of enolate anions.

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## References and Notes

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(11) The NMR ($CCl_4$) signal of the vinylic proton of *1* appeared at $\delta$ 4.40 as a sharp t, *J* = 7 Hz, and that of the *E*-isomer at 4.52, t, *J* = 7 Hz.

(12) L. Birkofer and H. Dickopp, *Chem. Ber.*, 102, 14 (1969).

(13) Analysis was performed with a crude reaction mixture.

(14) The NMR ($CCl_4$) spectrum showed the following signals: $\delta$ 1.03 (t, *J* = 7 Hz), 1.48 (dt, *J* = 1, 6.5 Hz), 2.02 (unresolved q, *J* = 7 Hz), 4.47 (q, *J* = 7 Hz), and the *E*-*Z* mixture exhibited additional signals at $\delta$ 1.55 (d, *J* = 7 Hz) and 4.52 (q, *J* = 7 Hz).

(15) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", 4, 310 (1974).

(16) The reaction did not proceed at -78 °C.

(17) Enol trimethylsilyl ether of 2-methylcyclohexanone could be equilibrated to 95% isomer at room temperature in the presence of 3 mol % of TBAF, but equilibration was greatly suppressed by addition of ethyl trimethylsilylacetate, which works as the scavenger of proton sourses.