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Stereochemical Consequences in the Deprotonation of Enoates

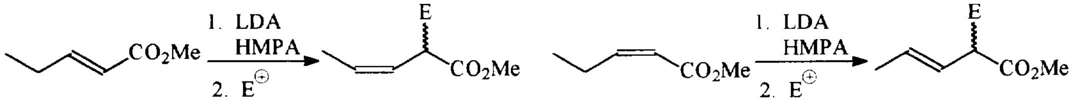
Paul Galatsis,*[1] **Jeffrey J. Manwell and Scott D. Millan**

Department of Chemistry and Biochemistry
University of Guelph
Guelph, Ontario, Canada N1G 2W1

ABSTRACT: A cyclic transition structure for the deprotonation of enoates was proposed to rationalize the geometry of the deconjugated olefin and the substrate reactivity patterns.

The deprotonation of carbonyl compounds to generate the corresponding enolate for use in the formation of carbon-carbon bonds plays a pivotal role in organic synthesis.[2] Everything from stereoelectronic effects of deprotonation,[3] the stereochemical control of enolate formation[4] and reactivity[2,5] to aggregation effects[6] have all been intensively investigated. The corresponding studies for enoate systems, by contrast, have received limited attention.[7] These systems have all the attributes cited above plus the added complications of α- versus γ-alkylation and control of the geometry of the deconjugated olefin (Scheme 1).

Scheme 1



While working on a deconjugative aldol-cyclization sequence for the construction of cyclic ethers,[8] we became interested in the factors that control the deprotonation and olefin geometry in enoates and enimides. Our initial studies[8] were in agreement with the limited known information,[7] however, as we probed deeper into these systems we found that all control of olefin geometry in chiral enimides[9] was lost.[10] In an effort to determine the factors involved in the deconjugation, we studied this reaction using a variety of substrates under different conditions and now wish to present our initial findings on this chemistry.

We began by probing the steric requirements imposed on the reaction by the size of the ester substituent (see Table 1). As one can see, in going from hydrogen (dianion) through to *t*-butyl resulted in inversion of configuration of the deconjugated olefin as had been observed in earlier work.[7,8] For the (E)-isomer there was little steric effect imposed by the ester substituent, however, a more dramatic effect was noted for the (Z)-isomer (see Table 1, entries 2 and 10).

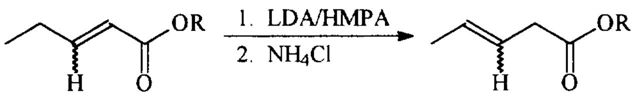


TABLE 1. Results From Ester Deconjugation

Entry	R	Substrate Geometry	Product Geometry (Z:E)	Yield (%)[a]
1	H	E	8 : 1	95
2	H	Z	1 : 43	95
3	Me	E	13 : 1	31[b]
4	Me	Z	1 : 20	13[b]
5	Et	E	13 : 1	76
6	Et	Z	1 : 21	76
7	*i*-Pr	E	15 : 1	64
8	*i*-Pr	Z	1 : 26	60
9	*t*-Bu	E	15 : 1	62
10	*t*-Bu	Z	1 : 12	80

a) isolated yields. b) low yield due to product volatility.

The effect of base and temperature on the deprotonation were also examined. As can be observed from Table 2, LHMDS consistently gave poorer selectivity in the deconjugation, while raising the temperature of the deprotonation above -40°C eroded the level of stereoselectivity of the deconjugated olefin.

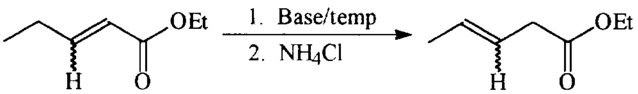
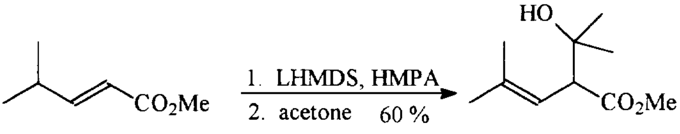


TABLE 2. Effect of Base and Temperature on Deconjugation.

Entry	Substrate Geometry	Base	Temp	Product Geometry (Z:E)	Yield (%)[a]
1	E	LDA	-78° C	13 : 1	76
2	Z	LDA	-78° C	1 : 21	76
3	E	LHMDS	-78° C	14 : 1	75
4	Z	LHMDS	-78° C	no rxn	-
5	E	LHMDS	-40° C	6 : 1	76
6	Z	LHMDS	-40° C	1 : 11	64
7	E	LHMDS	0° C	5 : 1	55
8	Z	LHMDS	0° C	1 : 2	69
9	E	LTMP	-78° C	no rxn	-
10	Z	LTMP	-78° C	1 : 21	76
11	E	LTMP	-40° C	13 : 1	66
12	Z	LTMP	-40° C	1 : 19	68
13	E	LTMP	0° C	4 : 1	55
14	Z	LTMP	0° C	1 : 10	62

a) isolated yields.

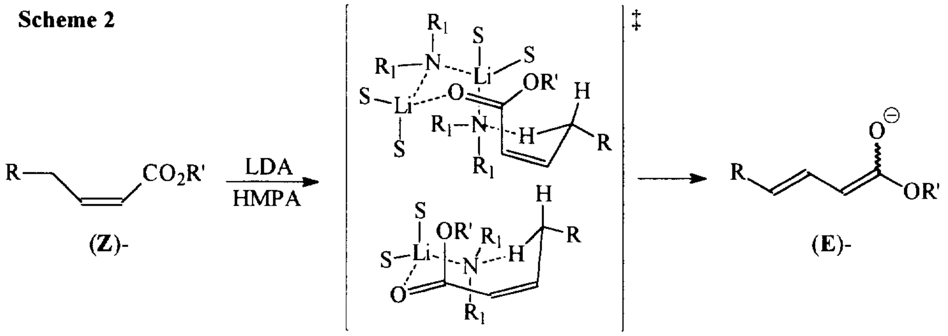
Simple carboxamides were investigated and proved to be problematic. They would either not react or they would undergo Michael addition of the base. However, we did find that N,N-diisopropyl (E)-2-pentenamide could be deconjugated with LDA but gave poor olefin selectivity (Z:E=1.5:1). We also noted that LHMDS/HMPA was the base of choice for the deconjugation of more substituted systems, such as ester **1**. No deconjugation was observed using LDA, but the reaction could be effected using LHMDS. HMPA played a critical role, since without it a yield of only 7% was seen for **2**.



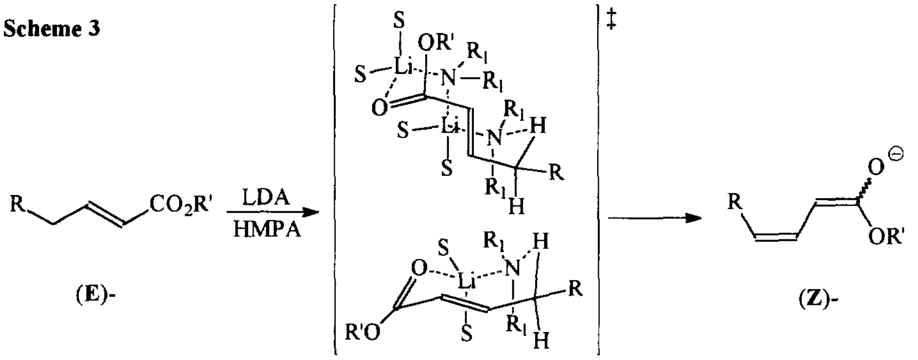
1 **2**

An initial rationalization for the stereochemistry of the deconjugation was put forward by Kende.[7d] In this explanation an acyclic transition state was proposed, in which, $A^{1,3}$ strain was the principle controlling factor. Our results clearly indicate that the situation is more complex. Furthermore, the nature of the base and cosolvents are important in this reaction. These reactions do not occur in the absence of HMPA. From the work of Collum and others,[11] it is known that in the presence of HMPA, LDA exists primarily as a dimer. Perhaps it is this complex that prevents the Michael addition and carries out the deprotonation. The proposed transition structures (Schemes 2 and 3) are consistent with the experimental observations. Each accounts for the inversion of the double bond geometry in the presence of the lithium amides. Furthermore, these structures also account for the improved reactivity when the base is changed to LHMDS in more substituted compounds. In these cases the longer C-Si and N-Si bonds of the base provides for a relief of 1,3-diaxial interactions between the substituents on the substrate and the groups on the amide base. Although LDA may exist primarily as a dimer, recent work by Streitwieser[12] has indicated that the deprotonation is 0.5 to 1.0 order in the base. While we know HMPA is critical in these reactions, one cannot ignore these observations, thus we include both monomer and dimer possibilities in this reaction. The optimal geometry for proton abstraction, best accommodated by an 8-membered ring,[13] is accomplished by the lithium amide

Scheme 2



Scheme 3



monomer. However, there are several examples in which the product stereochemistry can only be accounted for via a 10-membered ring.[14] Therefore, the structure in which a LDA dimer is the reactive species can be considered as a viable transition structure.

In summary, we propose that a cyclic transition state, containing either monomeric or dimeric lithium amide, is responsible for the observed inversion of double bond geometry in these systems. Work is in progress to further elucidate the nature of this transition structure.

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