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STEREOSELECTIVE DEPROTONATION OF α,β-UNSATURATED AMIDES

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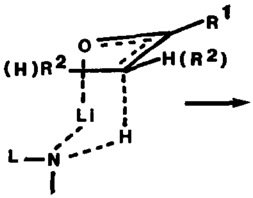
Abstract: Deprotonation of unsaturated amides **3c** - **f** occurs stereoselectively from the Z-γ-carbon leading, after methylation, to deconjugated products **4-6.** An eight membered ring transition state model analogous to the Ireland formulation for enolization is proposed to explain these observations.

The prediction of the stereochemistry of enolate formation is fundamental to the synthetic utility of a host of stereoselective C-C bond formation strategies of which the aldol condensation currently occupies a prominent position.[1] A reasonably large body of data[2] on enolization stereoselection may be rationalized by the pericyclic, chair-like transition state model proposed by Ireland.[3] In this model, which is well founded on conformational (allylic strain)[4] and stereoelectronic[3,5] considerations, deprotonation is depicted to occur perpendicular to the plane of the carbonyl group coordinated to the lithium dialkylamide, i.e., **1** → **2.**[6] Compelling kinetic[7] and spectroscopic[8] evidence for lithium base complexation **prior** to proton abstraction has been recently reported.



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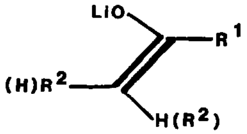

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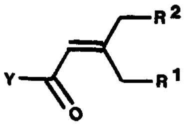
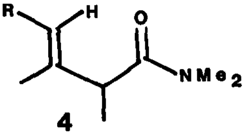


3

	Y	R^1	R^2
a	OMe	D	H
b	OMe	H	D
c	NMe_2	TMS	H
d	NMe_2	H	TMS
e	NMe_2	D	H
f	NMe_2	H	D

The question of stereoselection in dienolate formation of β,β-disubstituted α,β-unsaturated carbonyl derivatives, **3** has been only recently addressed in spite of the extensive synthetic use of such systems.[9] Numerous scattered reports,[10] primarily on unsaturated esters, do not allow unambiguous generalization concerning the **syn** vs anti **γ-H** site of deprotonation.[11] On the basis of a systematic study on **β-mono** substituted unsaturated esters,[12] it has been argued that the course of kinetic proton abstraction is determined by the relative stabilities of conformers leading to the intermediate dienolates. The recent report by Harris and Weiler[13] concerning the stereoselective deprotonation of specifically deuterated esters **3a** and **3b** prompts us to disclose our preliminary observations on the deprotonation of isomeric pairs of unsaturated amides **3c**,**3d** and **3e**,**3f**.[14]

The Z and γ-silylated amide **3c**[15] was subjected to deprotonation (1.1 equiv LDA/THF/RT/1h) followed by MeI quench and aq NH$_4$Cl work up to afford the deconjugated products **4a** and **5a** in a ratio of 79:21 (90% yield). Using identical conditions but the bulkier LiTMP as base gave **4a** and **5a** in a 70:30 ratio (84% yield). Stereochemical assignments rest on the precedented[16] vinyl H-allylic CH$_3$ coupling constants, J = 0.732 Hz for **4a** and J = 1.172 Hz for **5a**. Application of similar conditions to **3d** resulted in the formation of **6a** (72% yield; NMR (CDCl$_3$) δ 4.69, 4.77, 2 x s, 2H).



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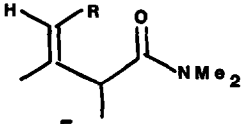

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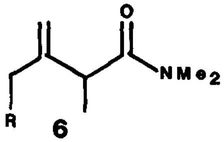
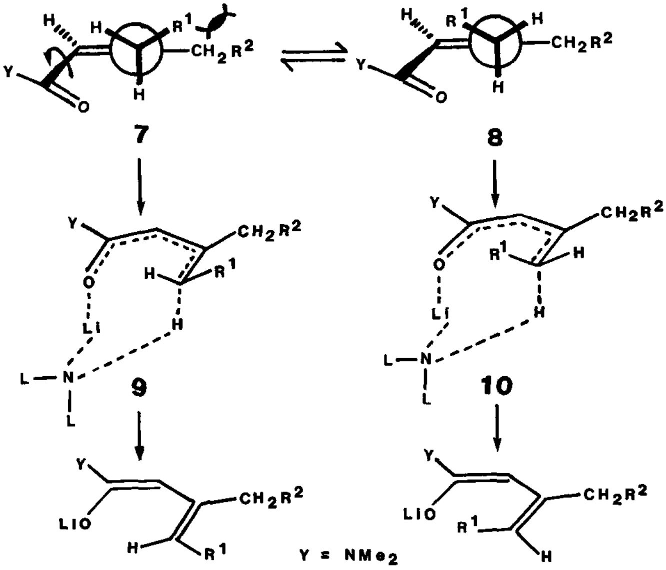


6

a: R = TMS; **b:** R = D

To remove the counteracting acidifying and steric effects of γ-silyl substituents on the deprotonation process, the monodeuterated unsaturated amides **3e**[17,18] and **3f**[18,19] were treated under similar reaction conditions (LDA as base) to those used for **3c** and **3d**. **3e** (69.5% d$_1$ in Z - Me) gave an unresolved mixture of **4b** and **5b** containing 67% d$_1$[20] while **3f** (78% d$_1$ in E - Me) produced **6b** containing 80% d$_1$ based on ^{1}H NMR integration. The ^{2}H NMR spectrum of **6b** showed deuterium only in the β-methyl group.



Scheme 1

These results demonstrate that β,β-disubstituted unsaturated amides **3c-d** undergo deprotonation exclusively from the Z -γ-carbon. Extrapolation from the conformational and transition state considerations applied to enolate deprotonation[2,3] leads to the formulation, expressed in **Scheme 1,** as corresponding operational models for the deprotonation of unsaturated carbonyl systems. In addition to the normal 1,3-allylic strain interactions,[4] the relative energies of conformers **7** and **8** are determined by the **s-cis** and **s-trans** amide function rotational isomer population ratio[21] which will impart an additional steric factor. Following initial reversible complexation of carbonyl oxygen with lithium dialkylamide,[8,22] the deprotonation step to the Z -and E -dienolates **11** and **12** proceeds via eight-membered ring transition states[23] **9** and **10** respectively analogous to the pericyclic Ireland model **(1)** except that lithium transfer to oxygen necessitates the additional requirement for the **s-cis** rotamers.

The results of deprotonation of the Z -silylated **3c** with LDA and LiTMP parallel those of Ireland[3] more closely than those of Heathcock[24] for the corresponding α-enolization of carbonyl systems. With both bases, the significant amide - $SiMe_3$ non-bonded interaction[25] renders more favorable transition state **9** over **10** (R^1 = $SiMe_3$, R^2 = H) leading predominantly to dienolate **11** over **12** [26] and hence product **4a** over **5a.** The slight decrease in the **4a:5a** product ratio using LiTMP (70:30) compared to LDA (79:21) can then be rationalized in terms of looser complexation with the more sterically demanding LiTMP thus allowing slightly more of the reaction to proceed via **9.** Exclusive formation of **6a** from **3d** in spite of the acidifying effect of silicon[27] negates the argument that this effect is responsible for the result observed for **3c.**

The results of deprotonation of **3e** and **3f** coupled with the work of Harris and Weiler[13] establish conclusively that for β,β-disubstituted carbonyl systems,[28] deprotonation occurs exclusively from the Z -γ-carbon[29]. The numerous questions raised by the hypothesis depicted in **Scheme 1** are under investigation[30].

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