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REGIOSELECTIVITY IN DEPROTONATION OF KETONE DIMETHYLHYDRAZONES WITH LITHIUM AMIDE BASES

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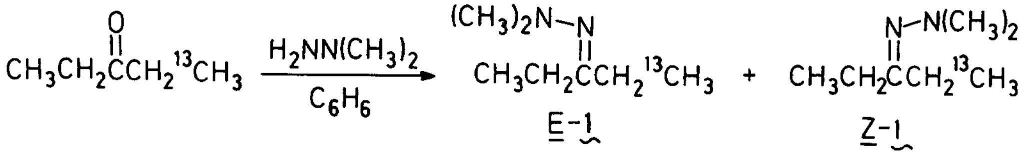
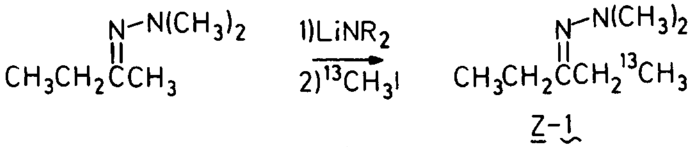
Abstract: The regiochemistry of deprotonation of 3-pentanone dimethylhydrazone by lithium amide bases has been studied by ^{13}C-NMR spectroscopy of ^{13}C-enriched samples.

The regioselectivity of formation of lithio anions by deprotonation of carbonyl compounds and their derivatives is of both theoretical and practical significance in organic chemistry. Recent studies by a number of groups including those of Fraser, Jung, Kofron, Lyle and Shapiro on deprotonation of imines,[1] nitrosoamines,[2] oximes,[3] and tosylhydrazones[4] have suggested that deprotonation generally occurs anti to the lone pair of the C=N nitrogen. An exception to this generalization had been work reported by Jung who reported kinetic deprotonation occurred syn to the C=N nitrogen lone pair of _Z_-1,1,1-trideutero-3-pentanone dimethylhydrazone using lithium diethylamide.[5] As an outgrowth of other experiments dealing with spectroscopic studies of the stereoselectivity of lithio anions of oxaallyl and azaallyl systems, we have now investigated the regioselectivity of deprotonations of ^{13}C-enriched 3-pentanone dimethylhydrazone (**1**) with lithium amide bases. Our results are not consistent with those first reported by Jung[5] and suggest that predictive generalizations regarding the regioselectivity of deprotonation of all C=N carbonyl derivatives cannot be made. As in previous studies, we employed ^{13}C NMR spectroscopy of ^{13}C-enriched samples to observe directly both the structure of the intermediate lithio anions and the products' distribution after alkylation.[6]

Our studies of deprotonation regioselectivity of ketone dimethylhydrazones employed _ca._ 30% enriched ^{13}CH$_3$ labeled 3-pentanone dimethylhydrazone. Following literature procedures, the reactions shown in equations 1 and 2 afforded samples of completely epimerized and >95%



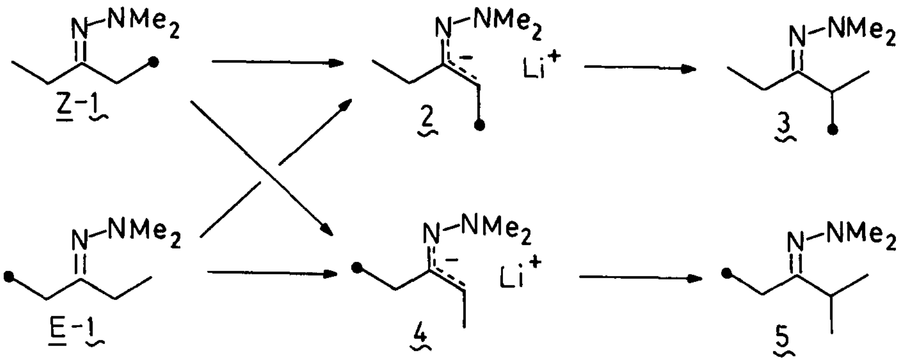
$$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2{}^{13}CH_3 \xrightarrow[C_6H_6]{H_2NN(CH_3)_2} \underset{E\text{-}\mathbf{1}}{CH_3CH_2\overset{(CH_3)_2N\frown N}{\overset{\|}{C}}CH_2{}^{13}CH_3} + \underset{Z\text{-}\mathbf{1}}{CH_3CH_2\overset{N\frown N(CH_3)_2}{\overset{\|}{C}}CH_2{}^{13}CH_3} \qquad (1)$$



$$CH_3CH_2\overset{N\frown N(CH_3)_2}{\overset{\|}{C}}CH_3 \xrightarrow[2)^{13}CH_3I]{1)LiNR_2} \underset{Z\text{-}\mathbf{1}}{CH_3CH_2\overset{N\frown N(CH_3)_2}{\overset{\|}{C}}CH_2{}^{13}CH_3} \qquad (2)$$

Z-$^{13}CH_3$-3-pentanone dimethylhydrazone, respectively.[7] The stereochemistry of the labeled dimethylhydrazones prepared according to these procedures was verified in each case by ^{13}C NMR (*E* + *Z*-**1**; two CH_3 peaks in an area ratio of 52:48 at δ10.2 and 10.0 relative to external TMS: *Z*-**1**; a singlet at δ10.0 relative to external TMS).

Scheme



The Scheme summarizes the possible regiochemical and stereochemical isomers that can be formed from dimethylhydrazones **1** by amide base deprotonation and subsequent alkylation with methyl iodide.[7] In order to determine directly how many possible lithio anions were actually formed and in order to minimize errors in determining relative abundances of isomeric species by area measurements which could result from different relaxation times or different nuclear Overhauser effects for $^{13}CH_3$ groups in different environments, our first control experiments involved deprotonation of an equal mixture of epimers *Z*-**1** and E-**1** with lithium diethylamide in THF at 0°C for 0.5 h. The resulting ^{13}C NMR spectrum showed only two peaks at δ11.6 and 13.3 which we assigned to the syn lithio anion **2** and the anti lithio anion **4**, respectively (*vida infra*). Addition of methyl iodide at -78°C to this mixture of lithio anions in turn led to an epimeric mixture of labeled 2-methyl-3-pentanone dimethylhydrazones **3** and **5** (Figure). Under the conditions of our experiments (alkylation at -78°C and immediate ^{13}C NMR observation of product at -50°C) the thermodynamically less favored C=N geometry shown for these 2-methyl-3-pentanone dimethylhydrazones would be expected.

Deprotonation of *Z*-**1** was then studied to determine the regioselectivity of dimethylhydrazone deprotonation. Lithium diethylamide in THF was allowed to react for 0.5 h at 0°C with *Z*-**1** to give a mixture of lithio anions by ^{13}C NMR (Figure). This mixture consisted of 48% syn lithio anion **2** and 52% anti lithio anion **4** based on the corrected areas of the peaks at δ11.6 and 13.3, respectively. Addition of methyl iodide to this lithio anion solution at -78°C then produced a 50/50 mixture of epimeric $^{13}CH_3$ labeled 2-methyl-3-pentanone dimethylhydrazones **3** and **5** (Figure).

Deprotonation of *Z*-**1** with lithium diisopropylamide for 0.5 h at 0°C showed that the regioselectivity of ketone dimethylhydrazone deprotonation can be slightly modified by the nature of

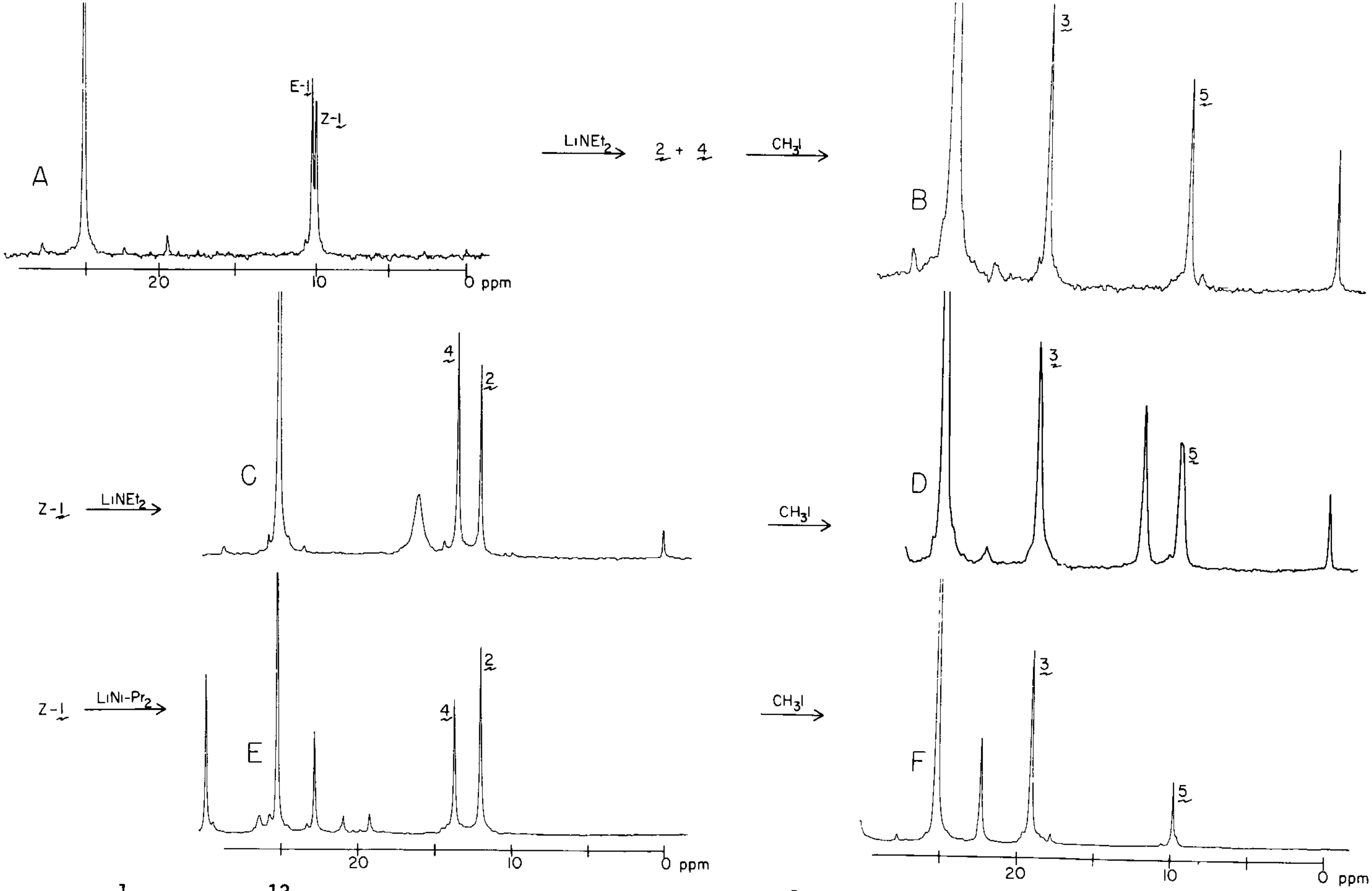


Figure. ^{1}H-decoupled ^{13}C NMR spectra recorded at 25 MHz at ca. -50°C: (A) equal mixture of E- and Z-1; (B) equal mixture of 3 and 5; (C) lithio anions 2 and 4 from deprotonation of Z-1 with lithium diethylamide; (D) mixture of 3 and 5 from methylation of lithio anions generated with lithium diethylamide; (E) lithio anions 2 and 4 from deprotonation of Z-1 with lithium diisopropylamide; (F) mixture of 3 and 5 from methylation of lithio anions generated with lithium diisopropylamide. Spectra C-F contain signals from excess amide and/or amine. All spectra contain the upfield signal from THF at δ25.1 relative to external TMS, and several contain the TMS signal at δ0.0. The internal consistancy of the ratios 2:4 and 3:5 indicate that errors in area measurements caused by overlap of impurity signals with the signals of interest are negligible.

the amide base. In this lithium diisopropylamide deprotonation, a mixture of 72% syn lithio anion **2** and 28% anti lithio anion **4** was formed. Addition of methyl iodide to this solution of lithio anions at -78°C then yielded a mixture of $^{13}CH_3$ labeled 2-methyl-3-pentanone dimethylhydrazones consisting of 75% **3** and 25% **5** (δ18.9 and 9.6 relative to external TMS) (Figure). Isomers **3** and **5** were readily distinguished by the expected large chemical shift difference for a $^{13}CH_3$ group in an isopropyl versus an ethyl environment. Since **3** was the predominant product formed by methylation of the unequal mixture of lithio anions **2** and **4** formed by LDA deprotonation, we have assigned structure **2** to the predominant lithio anion. Estimated errors in determining the relative abundances of these and other isomeric dimethylhydrazones and lithio anions are ±5%.

These results indicate that the geometry of the C=N nitrogen lone pair or substituent group has only a small effect on the site of kinetic deprotonation, at least for dimethylhydrazones with otherwise sterically and electronically equivalent acidic protons. Thus minor changes in the conditions for the deprotonation reactions or in the nature of the amide base used can have a measurable effect on the regiochemistry of these deprotonation reactions. Once formed, facile C-N isomerization apparently occurs in these lithio anions at 0°C within 0.5 h since we only observe Z C=N alkylated product in accord with previous results in related systems.[8,9]

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References and Notes

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7. Based on the facts that we only see two signals for the $^{13}CH_3$ groups and that two isomeric labeled 2-methyl-3-pentanone dimethylhydrazones are produced after methylation of the intermediate lithio anions, we have assumed an E_{C-C} geometry for the intermediate lithio anions. Similar C-C geometry has been observed or assumed for other azaallyl and oxaallyl lithio anions formed by kinetic deprotonations with amide bases.[6] This assumption does not materially affect our arguments about deprotonation regiochemistry.
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