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HIGHLY REGIOSELECTIVE DEPROTONATIONS OF ACYCLIC KETIMINES

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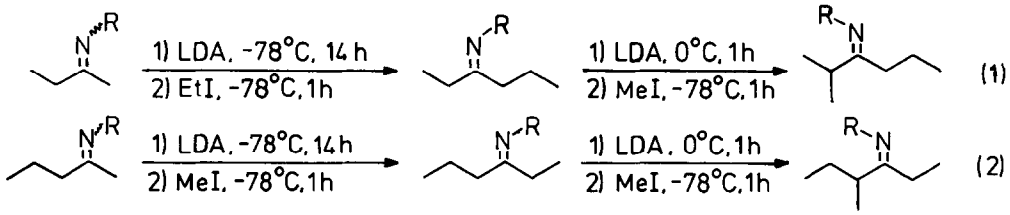
Abstract: Synthetic methods for highly regioselective deprotonation of methyl n-alkyl, n-alkyl n-alkyl, and n-alkyl sec-alkyl ketimines are described which permit electrophilic substitution at either structurally isomeric or stereoisomeric positions of ketimines derived from unsymmetrical acyclic ketones.

Control of regioselectivity in deprotonation and subsequent electrophilic substitution of carbonyl compounds and their derivatives is synthetically critical whenever unsymmetrical ketones or ketone derivatives are used as starting materials in syntheses involving enolates or azaallyllithium reagents. For example, in ketones formation of a specific enolate by proper choice of reagents has been reported recently.[3] Alternatively, hindered lithium dialkylamide bases can sometimes be used to deprotonate exclusively the less-substituted position of a ketone, and equilibration of enolates can also be used to form the thermodynamically favored more substituted enolate.[4] Direct formation of methylene enolates by carbon-carbon bond formation using acid chlorides and titanium methylene complexes is a new solution to the problem of regioselective enolate formation.[5]

Regioselectivity in deprotonation of the nitrogen derivatives of ketones is substantially more complicated than similar ketone deprotonations.[6] Since ketimines have some advantages in synthesis over simple ketone enolates (e.g. the potential for asymmetric syntheses),[7] methods to form azaallyllithium reagents regioselectively from ketimines could be very useful. In this report we describe experimental procedures developed in our research groups in which such regioselective control can be accomplished. Using procedures described below, deprotonation can be achieved at the $-CH_3-$ group of a methyl n-alkyl ketimine or at either the $-CH_2-$ or -CH- group of an n-alkyl sec-alkyl ketimine. Kinetically controlled deprotonations in which two different $-CH_2-$ groups are differentiated are also described.

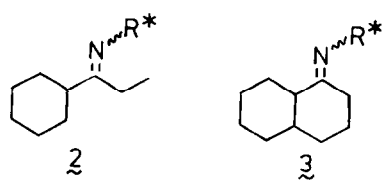
Regioselective deprotonation at the methyl position of methyl alkyl ketimines can be accomplished by carrying out such deprotonations at -78 °C (THF) with either lithium diisopropylamide (LDA) or lithium diethylamide (LDEA) regardless of the alkyl substituent on nitrogen or the C=N geometry of the ketimine.[6] At 25 °C, deprotonation occurs mainly anti to the nitrogen substituent. Thus, the kinetic product from a deprotonation-alkylation sequence starting with an acetone ketimine (i.e. the $Z_{C=N}$ ketimine isomer, see below) can be deprotonated at the remaining methyl position at either -78 °C or at 25 °C.

Regioselective deprotonation of di-n-alkyl ketimines is more problematic. In these cases it is necessary to use one stereoisomer of the ketimine which can be formed in situ from a deprotonation-alkylation sequence. The best results are obtained with a small nitrogen substituent, LDA as the base and 0 °C as the deprotonation temperature. For example, the Z-3-hexanone ketimine, prepared stereospecifically in situ, can be deprotonated with LDA at 0 °C and methylated with methyl iodide at -78 °C to form the ketimine of 2-methyl-3-hexanone (equation 1). Alternatively, 4-methyl-3-hexanone ketimine is the product when the steps in equation 2 are used. With LDA and n-butyl or cyclohexyl as the R group on nitrogen, the products are obtained with >50:1 regioselectivity. Care must be taken, however, to avoid thermal isomerization of the stereochemically pure ketimines arising from the first alkylation step.[8]

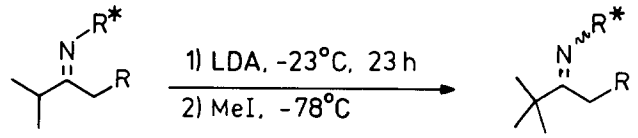


Confirmation that 0 °C deprotonation using LDA of stereoisomerically pure ketimines can occur with high regioselectivity anti to the nitrogen alkyl substituent was obtained using $^{13}CH_3$-labeled ketimines of 3-pentanone. In these cases, LDA was used as the base and n-butyl and cyclohexyl groups were used as nitrogen substituents. As has been discussed previously,[6] the final products in such experiments using $^{13}CH_3$ labels are isomeric by virtue of having a $^{13}CH_3$ group in an ethyl or isopropyl position and can be readily distinguished by ^{13}C NMR spectroscopy. Deprotonation anti to the nitrogen n-butyl or cyclohexyl group occurred with 10:1 regioselectivity. Our previous studies of di-n-alkyl ketimines have shown that use of more sterically demanding alkyl groups as nitrogen substituents (e.g. tert-butyl, phenyl) or the use of the less hindered LDEA in place of LDA leads to lower regioselectivity.[6]

These methods for regioselective deprotonations can be extended to other systems containing chelating groups on the nitrogen substituent. In these cases, reaction sequences can be used to form quaternary carbon centers regiospecifically (eq. 3). Indeed, the procedures in equations 3 and 4 permit regioselective discrimination between the -CH- and $-CH_2-$ groups of acyclic ketimines. Attempts to extend these methods to cyclic systems such as the ketimines **2** or **3** failed in that $-CH_2-$ rather than -CH- deprotonation occurred.



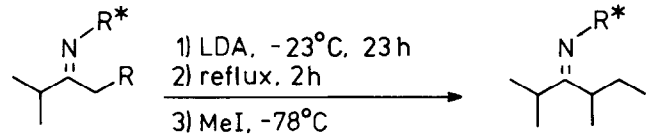
2 3



(3)

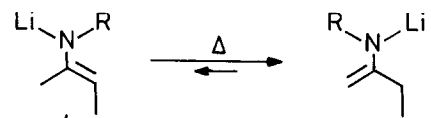
1a R = C_2H_5
b R = CH_3

R* = (S)-$CH(CH_2C_6H_5)CH_2OCH_3$



(4)

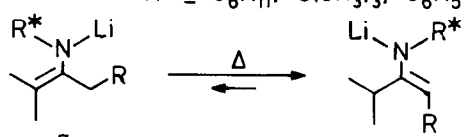
In cases where the azaallyllithium reagents derived from ketimines exist as two structural isomers in which one of the azaallyllithium reagents is less substituted than the other, it is also possible to control the structure of the azaallyllithium reagent using thermodynamic control. Specifically, heating azaallyllithium reagents (THF, 25 °C, 24-48 h) such as **4** and **5** or the lithio derivatives of **1a** results in equilibration of the structurally isomeric azaallyllithium reagents and predominant formation of the less substituted species (eq. 5 and 6).



(5)

4

R = c-C_6H_{11}, -$C(CH_3)_3$, -C_6H_5

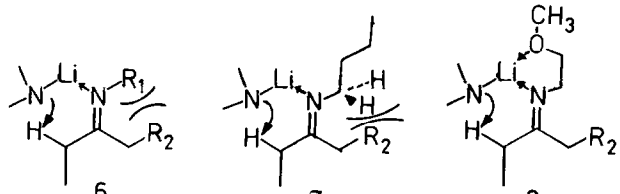


(6)

5

The stereochemical orientation of protons on the α-carbon of a ketimine relative to the substituent on the nitrogen atom and the degree of substitution of the α-carbon are the two most obvious ways of kinetically differentiating between azaallyllithium formation at the two regioisomeric positions of a ketimine. Fraser and Houk have shown that the nitrogen substituent of a ketimine prefers the syn orientation in the derived azaallyllithium reagent.[9] Nevertheless, studies have shown that this thermodynamic preference for the Z_{C-N} azaallyllithium reagent does not substantially affect the early transition state for the expected exothermic deprotonation reaction of a ketimine by a lithium dialkylamide.[6] Furthermore, steric interactions of the hindered lithium base and the ketimine have been previously been shown to be the primary factors which determine regioselectivity in ketimine deprotonation. Our previous results were rationalized by a transition state model (**6**) in which the coordination of the hindered lithium dialkylamide base to the ketimine nitrogen occurs and deprotonation follows via a closed transition state analogous to those postulated for stereoselective deprotonations of esters,[10] ketones,[11] oxazolines[12] and aldehyde dimethylhydrazones.[13] Exceptions to the regioselective deprotonation anti to the nitrogen substituent predicted by this model were explained by 1,3-allylic interactions between the R_1 groups on the nitrogen substituent and the R_2 groups on the ketimine which destabilized the transition state. The results reported

herein are also accommodated by this transition state model. Although smaller alkyl substituents on the nitrogen atom of a ketimine such as an n-butyl group are not as sterically demanding as a tert-butyl group, the smaller n-butyl affords more regiochemical control in deprotonation because the R_1 substituent in this case contains a methylene group bonded to nitrogen. This minimizes the 1,3-allylic interactions which would otherwise destabilize the transition state (e.g. **7**). In the case of nitrogen substituents containing a β-methoxy group, chelation by oxygen would be expected to further stabilize the closed transition state **8**. The result in both of these cases is useful regiochemical control of the kinetic deprotonation products. Thermodynamic control of the regiochemistry of these azaallyllithium reagents which is opposite to that seen for lithium enolates of ketones can also be rationalized if one considers azaallyllithium reagents to have greater carbanion character than oxaallyllithium reagents (lithium enolates). If true, the less substituted azaallyllithium reagent (i.e. the less substituted carbanion) would be expected to be more stable.



6 7 8

In summary, by judicious selection of the nitrogen substituent, the base, and the reaction temperature, deprotonations of acyclic ketimines can be accomplished with high regioselective discrimination between the two α positions.

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