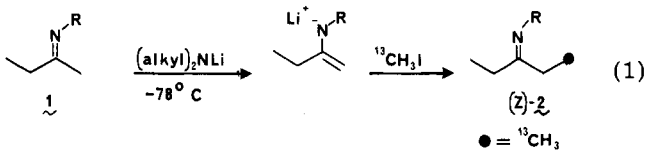
Regioselectivity in Deprotonation of Imines Derived from 3-Pentanone

Summary: Regioselectivity in deprotonation of (*Z*)-*tert*-butyl, (*Z*)-cyclohexyl, (*Z*)-benzyl, and (*Z*)-phenyl ketimines of 3-pentanone has been shown to be generally low and variable. Deprotonation of $^{13}CH_3$-labeled *Z* ketimines with either lithium diisopropylamide or lithium diethylamide in THF and methylation at −78 °C was used to determine regiochemistry. Syn/anti deprotonation ratios varied from 74/26 to 22/78 with different ketimines and different bases.

Sir: Metalated imines and related species have become synthetically important alternatives to simple ketone enolates.[1-3] However, in spite of numerous synthetic applications of these reagents, there is a surprising lack of information about the stereoselectivity and regioselectivity of their formation in deprotonation reactions. In light of our recent studies on regioselectivity in deprotonation of ketone dimethylhydrazones,[4-6] we have undertaken a study to determine the extent of regioselectivity, if any, in deprotonation of a series of 3-pentanimines. Our results discussed below clearly show that the 1-azaallyllithium reagents are kinetically formed with low regioselectivity and that what regioselectivity is seen is a function both of the *N*-alkyl group of the alkyl ketimine and of the structure of the hindered lithium dialkylamide base used in the deprotonation.[7]

We have prepared $^{13}CH_3$-labeled ketimines with defined C=N stereochemistry for use in our regiochemistry studies using the procedure of eq 1. Deprotonation of ketimines



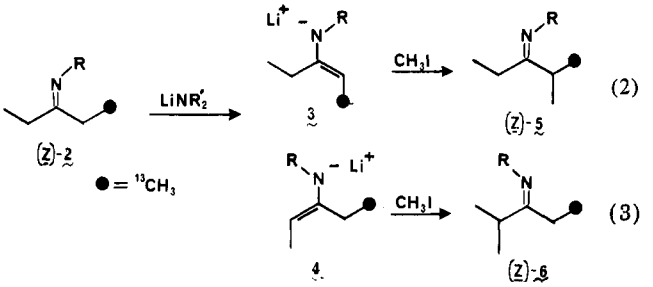
(1)

of 2-butanone (1) at −78 °C gave the (*Z*)-azaallyllithium species (R syn to the charged carbon, vide infra). Subsequent methylation with 30% ^{13}C-enriched methyl iodide gave (*Z*)-**2** as the only labeled species detectable by ^{13}C NMR. When (*Z*)-**2** was allowed to stand at 25 °C, isomerization to a mixture of (*E*)- and (*Z*)-**2** occurred. In each case, the signal from the labeled methyl group of (*Z*)-**2** was downfield from that of the labeled methyl group of (*E*)-**2** (Table I). The regiochemistry of deprotonation of the ketimines (*Z*)-**2** was then followed by alkylating the intermediate azaallyllithium reagents with methyl iodide and examining the methylation products by ^{13}C NMR spectroscopy. The method (eq 2 and 3) is analogous to that

Table I. ^{13}C-Labeled Methyl Chemical Shifts[a]

R	chemical shift (*Z*)-2	(*E*)-2	3	4	(*Z*)-5	(*E*)-5	(*Z*)-6	(*E*)-6
tert-butyl	10.8	10.1	13.4[b]		18.8	20.5	10.6[c]	10.9[c]
c-C_6H_{11}	11.5	10.3	13.8[b]		19.2	19.6	9.8	11.3
phenyl	12.2	11.9	*d*	*d*	19.0	19.6	9.4	10.8
benzyl	10.0	9.5	13.9	12.9	18.5	19.5	9.5	10.0

[a] Chemical shifts in δ units: the β-carbon signal of THF is defined as δ 25.0. [b] The signals for the two anions were not resolved. [c] The equilibrium ratio of (*Z*)-**6** and (*E*)-**6** measured by ^{13}C NMR was 25:75. [d] Not measured.



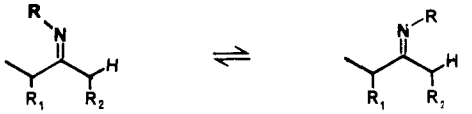
(2) (3)

used in our earlier ketone dimethylhydrazone studies.[6] Table II lists the regioselectivity we observed in several deprotonation reactions using either lithium diethylamide (LDEA) or lithium diisopropylamide (LDA) as a base.

As can be seen from the data in Table II, there were significant differences in regioselectivity for deprotonation of different ketimines. The *tert*-butyl and phenyl ketimines both seemed to favor anti deprotonation while the benzyl ketimine favored syn deprotonation. Only modest regioselectivity was observed in either case. Regioselectivity in deprotonation of the cyclohexyl ketimine with LDEA was essentially zero. Minor differences in deprotonation regioselectivity for ketimines were seen when LDEA was substituted for LDA in the deprotonation step.[7]

The low regioselectivity we observed in these deprotonations did not result from prior isomerization of the ketimine (*Z*)-**2**. When the deprotonation of (*Z*)-**2** was monitored by ^{13}C NMR spectroscopy, no (*E*)-**2** could be detected except in the deprotonation of (*Z*)-**2** (R = *tert*-butyl) with LDA wherein we observed ca. 15% isomerization of (*Z*)-**2** to (*E*)-**2** when the deprotonation reaction was ca. 75% complete.

Our results from the methylation experiments confirmed the previous reports that the azaallyllithium reagents formed in deprotonation of ketimines are syn.[8] We typically observed that alkylation of the intermediate heteroallyllithium reagents **3** and **4** with methyl iodide produced the thermodynamically less stable imines (*Z*)-**5** and (*Z*)-**6**. Subsequent thermal isomerization produced the *E* imine products (eq 4). *tert*-Butyl ketimines, which have the


(4)

(*Z*)-**5**, R_1=$^{13}CH_3$, R_2=CH_3 (*E*)-**5**, R_1=$^{13}CH_3$, R_2=CH_3

(*Z*)-**6**, R_1=CH_3, R_2=$^{13}CH_3$ (*E*)-**6**, R_1=CH_3, R_2=$^{13}CH_3$

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0022-3263/81/1946-3157$01.25/0

Table II. Regioselectivity in Deprotonation of Ketimines of 3-Pentanone[a]

R in (Z)-2	base	deprotonation temp, °C	rel % yield[b,e] 5	6
t-C_4H_9	LDEA	3	22	78[c]
t-C_4H_9	LDA	3	30	70[c]
$CH_2C_6H_5$	LDA	25	74	26[d]
c-C_6H_{11}	LDEA	0	53	47[d]
C_6H_5	LDA	25	25	75[d]
C_6H_5	LDEA	25	38	62[d]

[a] Deprotonations of (Z)-2 (ca. 0.25 M) were carried out at the indicated temperature by using ca. 2 equiv of the specified lithium dialkylamide base (ca. 0.5 M) in THF. Methylation was carried out at −78 °C. [b] Ratios of 5 to 6 were measured by comparison of $^{13}CH_3$-labeled isopropyl groups to ^{13}C-labeled ethyl groups (cf. ref 6). For R = benzyl, signals from 3 and 4 were resolved, and their ratio as measured from $^{13}CH_3$ peak areas of labeled methyl groups agreed with the ratio of 5 to 6 determined after methylation. [c] These ratios are the corrected ratios of the products 5 and 6. [d] These ratios are the uncorrected ratios of the areas of the ^{13}C NMR signals ascribed to 5 and 6; we typically observed in this work and previously[4] that the peak area ratios differ by less than 10% from the corrected 5 to 6 ratios. [e] Yields of isopropyl ethyl ketimines measured in comparable methylations of the unlabeled azaallyllithium reagent derived from diethyl ketimine with unlabeled methyl iodide were measured by GC using an internal standard and are >95%.

largest steric demands, were studied in some detail to confirm the syn stereochemistry of the intermediate azaallyllithium reagents. When unlabeled 2 was deprotonated and the resulting intermediate (unlabeled 3) was treated with ^{13}C-labeled methyl iodide, we obtained (Z)-5 (δ 18.8) which isomerized on standing to give predominantly (E)-5 (δ 20.5). Further, when N-(tert-butyl)-3-methyl-2-butanimine was deprotonated and subsequently treated with ^{13}C-labeled methyl iodide, we obtained only (E)-6 (δ 10.9); on standing some (Z)-6 (δ 10.6) formed, but (E)-6 always predominated. It is apparent from our results that the previously described preference for syn structures in cyclic azaallyllithium reagents obtains in these acyclic cases as well but that this anion stability has little influence on the transition state for the deprotonation reaction. Indeed, the transition state for this type of exothermic reaction is not likely to be very productlike, and other factors such as steric accessibility of the weakly acidic protons are apparently as important as the stability of the incipient azaallyllithium reagent.

The results described above suggest a complicated picture for regioselectivity in imine deprotonations. Previously, deuterium incorporation (KO-t-Bu, Me_2SO-d_6) into N-benzyl-2-propanimine had suggested that deprotonation occurred only syn to the nitrogen alkyl group,[9] but a recent report that protonation of azaallyllithium reagents by methanol produces nearly quantitative yields of secondary enamines shows that H/D exchange experiments may not provide reliable information concerning deprotonation regioselectivity.[10] The work reported herein and our previous studies of regioselectivity in ketone dimethylhydrazone deprotonations[4,6] clearly show that regioselectivity in deprotonation of nitrogen derivatives of carbonyl compounds is not subject to any simple generalizations. More extensive kinetic and NMR studies to determine the factors responsible for regioselectivity in imine deprotonation are in progress and are certainly necessary for a complete understanding of the effects seen above. Nevertheless, it is clear from our present studies that regioselectivity in formation of azaallyllithium reagents from imines is variable to a greater extent than previously expected and that such regioselectivity is significantly affected by relatively minor experimental changes.

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM 26268) and the Robert A. Welch Foundation. The Varian FT-80 NMR spectrometer used in this research was purchased with the aid of NSF Grant No. CHE-77-09279 to Texas A&M University.

Registry No. 1 (R = *tert*-Bu), 78004-43-0; 1 (R = c-C_6H_{11}), 6125-75-3; 1 (R = C_6H_5), 40296-03-5; 1 (R = $CH_2C_6H_5$), 31776-80-4; (E)-2 (R = *tert*-Bu), 78004-44-1; (Z)-2 (R = *tert*-Bu), 78004-45-2; (E)-2 (R = c-C_6H_{11}), 78004-46-3; (Z)-2 (R = c-C_6H_{11}), 78004-47-4; (E)-2 (R = C_6H_5), 78004-48-5; (Z)-2 (R = C_6H_5), 78004-49-6; (E)-2 (R = $CH_2C_6H_5$), 78004-50-9; (Z)-2 (R = $CH_2C_6H_5$), 78004-51-0; (E)-5 (R = *t*-Bu), 78004-52-1; (Z)-5 (R = *t*-Bu), 78004-53-2; (E)-5 (R = c-C_6H_5), 78004-54-3; (Z)-5 (R = c-C_6H_5), 78004-55-4; (E)-5 (R = C_6H_5), 78004-56-5; (Z)-5 (R = C_6H_5), 78004-57-6; (E)-5 (R = $CH_2C_6H_5$), 78004-58-7; (Z)-5 (R = $CH_2C_6H_5$), 78004-59-8; (E)-6 (R = *t*-Bu), 78004-60-1; (Z)-6 (R = *t*-Bu), 78004-61-2; (E)-6 (R = c-C_6H_{11}), 78004-62-3; (Z)-6 (R = c-C_6H_{11}), 78004-63-4; (E)-6 (R = C_6H_5), 78004-64-5; (Z)-6 (R = C_6H_5), 78004-65-6; (E)-6 (R = $CH_2C_6H_5$), 78004-66-7; (Z)-6 (R = $CH_2C_6H_5$), 78004-67-8.

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Synthesis of *N*-Glycosides. Formation of Glucosylamine by Reaction of 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose with Acetonitrile in the Presence of Trifluoromethanesulfonic Anhydride

Summary: The synthesis of glucosylamine by reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with acetonitrile in the presence of trifluoromethanesulfonic anhydride was shown to proceed through an intermediate oxazoline.

Sir: We reported recently a new method for the synthesis of glycosylglycosides[1] and *O*-glycosyl amino acids,[1,2,4] based on the peculiar property of trifluoromethanesulfonic (triflic) acid to form a stable, insoluble hydroxonium trifluoromethanesulfonate $F_3CSO_3^-H_3O^+$, which provides a very efficient trapping of the water liberated during the glycosylation reaction.[3] In this communication we show that, when 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1) was allowed to react at 0 °C for about 1 h in acetonitrile instead of dichloromethane in the presence of triflic anhydride, 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosylamine (3)

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