Stereoselective Formation and Electrophilic Substitution of Aldehyde Hydrazone Lithio Anions

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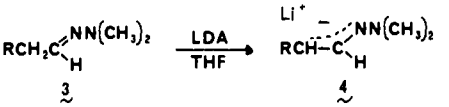
Abstract: The stereochemistry of the lithio anions (**4**) formed by deprotonation of aldehyde dimethylhydrazones ($RCH_2CHNN(CH_3)_2$; R = H, C_6H_5, $Si(CH_3)_3$) has been determined by ^1H NMR spectroscopy and trapping experiments. Deprotonation by lithium diisopropylamide (LDA) in tetrahydrofuran (THF) or LDA in THF with hexamethylphosphoric triamide (HMPA) gave anionic species **4** with *E* stereochemistry about the C_1–C_2 (R = C_6H_5, $Si(CH_3)_3$) bond and predominant *Z* stereochemistry about the C–N bond. For propionaldehyde dimethylhydrazone (R = CH_3), LDA/THF deprotonation gave >95% E_{C-C},Z_{C-N} lithio anion without any detectable Z_{C-C},E_{C-N} lithio anion, but deprotonation with LDA/THF/HMPA gave a 15/85 mixture of the two lithio anions, respectively. Deprotonation of the chiral propionaldehyde hydrazone made from (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) and propionaldehyde with LDA/THF gave the E_{C-C},Z_{C-N} lithio anion (>98%) while deprotonation with LDA/THF/HMPA gave the Z_{C-C},E_{C-N} lithio anion (>95%). Benzylation and hydrolysis of these two anionic species gave (*S*)-2-methyl-3-phenylpropanal (82% ee) and (*R*)-2-methyl-3-phenylpropanal (10% ee), respectively. Deprotonation of the chiral SAMP hydrazone of phenylacetaldehyde gave predominantly the E_{C-C},Z_{C-N} lithio anion which was methylated with 66% stereoselectivity. Thus, in two-step asymmetric electrophilic syntheses employing chiral aldehyde hydrazones the deprotonation step is seen to be more stereoselective than the alkylation step. Models for the transition states involved in LDA deprotonations of monosubstituted carbonyl compounds and derivatives in the presence and absence of HMPA are presented.

Carbon–carbon bond formation using stabilized carbanions is a fundamental reaction in organic synthesis. Work in a number of laboratories has broadened the scope of this type of carbon–carbon bond forming reaction through the introduction of soluble hindered bases and enolate equivalents or derivatives which afford high regioselectivity or high stereoselectivity.[2] Lithio salts of aldehyde or ketone dimethylhydrazones are a recent example of such an enolate equivalent and are readily prepared by deprotonation of dimethylhydrazones with hindered amide bases.[3a] These lithio dimethylhydrazone anions are stable at ambient temperatures with respect to decomposition or self-condensation and have been shown to react with a variety of electrophiles in high synthetic yield and with good regioselectivity in appropriate cases. Cleavage of the dimethylhydrazone products of these electrophilic substitution reactions can be readily accomplished with cupric chloride, ozone, or other mild procedures to regenerate a substituted carbonyl compound.[3a] In recent work, Enders and Eichenauer have shown that related chiral hydrazones prepared from a carbonyl compound and (*S*)-1-amino-2-methoxymethylpyrrolidine can be used in successful electrophilic asymmetric syntheses.[3b-d] In this paper, we describe the results of our studies of the stereochemistry of formation of the reactive intermediate lithio salts of aldehyde hydrazones. We have been able to show that substantial stereoselectivity is observed in deprotonations carried out either in THF or THF/HMPA using lithium diisopropylamide as a base. The case of propionaldehyde hydrazones is particularly interesting in that a change in the solvent used for these lithium diisopropylamide deprotonations from THF to THF/HMPA reverses the stereoselectivity observed in the deprotonation reaction so that either the *E* or *Z* lithio anion can be formed preferentially. We have also been able to show that application of these results to deprotonation of a chiral hydrazone derivative of propionaldehyde leads to a change in the sense of the asymmetric synthesis. This latter result is consistent with an asymmetric synthesis involving two independent stereoselective steps.

Some of the details of the deprotonation reactions of hydrazones and the stereochemistry and regiochemistry of the resulting lithio anions are known. In ketone dimethylhydrazones, the less substituted α carbon is generally deprotonated unless a second electron-withdrawing group (e.g., phenyl) is present.[3,4] In the case of ketone dimethylhydrazones, the predominant isomer of the lithio anion appears to be the isomer with the dimethylamino group syn to the deprotonated alkyl group.[4] In a preliminary account of a portion of this work, we reported that the predominant isomer of several aldehyde dimethylhydrazone lithio anions has similar *Z* stereochemistry about the C–N bond and that carbon–carbon bond rotation of these lithio anions is slow on the NMR time scale.[5] Some stereoselectivity in deprotonation reactions leading to these hydrazone lithio anions was also described in our communication.[5]

Results

Aldehyde Dimethylhydrazones. We have used ^1H NMR spectra and trapping experiments with electrophiles to characterize the anionic species formed by deprotonation of the aldehyde dimethylhydrazones **3**.[6] The ^1H NMR spectra of



3 **4**

a: R = H–
b: R = CH_3–
c: R = C_6H_5–
d: R = $(CH_3)_3Si$–

solutions of **4** contained large signals from solvents in the high-field region, and we could only observe signals from the formyl proton of **4a–d** and those from the benzyl and phenyl protons of **4c**. However, from the coupling constants of the formyl proton we can assign stereochemistry about the C_1–C_2 bond of **4b–d**. Electrophilic substitution of **4** at C_2 will give a substituted neutral product in which the stereochemistry about the C–N bond is the same as that in **4** if electrophilic substitution is faster than isomerization about the C–N bond in **4** and

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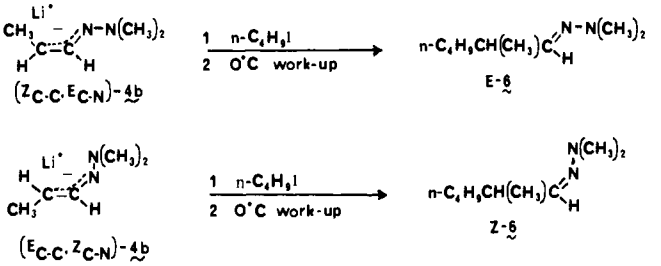
if the substituted product does not isomerize about the C–N bond. Since these two conditions are met in our procedures (vide infra), we were able to confirm the stereochemistry about the C–N bond in **4a,b** determined by ^{1}H NMR spectroscopy of the lithio anions by trapping experiments.

Aldehyde dimethylhydrazones are conveniently deprotonated by treatment with LDA in tetrahydrofuran,[3] but under these conditions species **4** precipitate from solution. Addition of 2.0 equiv of HMPA per lithium ion gives solutions of **4** which are suitable for ^{1}H NMR spectroscopy. Alternatively, deprotonation of **3** by LDA in the presence of HMPA leads directly to solutions of **4**. The solutions of **4a,c,d** showed no change in their ^{1}H NMR spectra upon standing at ambient temperatures for several hours. Solutions of **4b** in the presence of HMPA, however, were found to decompose rapidly at room temperature as determined by ^{1}H NMR, and we subsequently maintained these solutions below −12 to −20 °C. It is noteworthy that solid **4b** formed in the absence of HMPA appears to be stable at room temperature.

The ^{1}H NMR spectrum of **4a** prepared by either of the above methods contains two doublets of doublets centered at δ 6.6 (J_{cis} = 7.9, J_{trans} = 13.8 Hz) and 6.9 (J_{cis} = 8, J_{trans} = 15 Hz) in a ratio of ca. 89:11. The observed coupling constants in both cases are consistent with those expected for *Z* and *E* vicinal protons[7] and reinforce our assumptions that coupling constants to the formyl protons may be used to assign stereochemistry. Since sharp peaks are observed in the spectrum, both C–C and C–N bond rotations are slow; the activation energies for each isomerization must be higher than 16 kcal/mol.

Trapping experiments indicate that the predominant isomer about the C–N bond in **4a** is *Z*. Treatment of either suspended **4a** made without HMPA or a solution of **4a** containing 2.0 equiv of HMPA per lithium ion with 1-iodobutane at −78 °C followed by warming led to a mixture of (*E*)- and (*Z*)-hexanal dimethylhydrazones (**5**) in ca. 70% isolated yield. When care was taken to keep all solutions at ca. 0 °C (see Experimental Section), the ratios of *E*/*Z* products were determined by ^{1}H NMR to be 10/90 and 11/89, respectively, from **4a** made without and with HMPA. This ratio was conveniently determined by integration of the triplets for the formyl protons of *E*-**5** at δ 6.61 and *Z*-**5** at δ 6.96. When the mixture of *E*- and *Z*-**5** was allowed to stand at room temperature for 48 h, the ^{1}H NMR signal at δ 6.96 (*Z* isomer) disappeared. Similarly, treatment of a suspension of **4a** with chlorotrimethylsilane at −78 °C followed by warming produced a mixture of (*E*)- and (*Z*)-trimethylsilylacetaldehyde dimethylhydrazones (**3d**) with an *E*/*Z* ratio of 11:89 as determined by ^{1}H NMR analysis of the crude product. In this case the formyl, C_1, and dimethylamino proton signals from *E*- and *Z*-**3d** were distinct. In a preparative reaction *E*-**3d** was isolated in 59% yield after distillation. The mixture of *E*- and *Z*-**3d** also was completely converted to *E*-**3d** by gas chromatographic purification. Our observation that *Z*-**4a** predominates is consistent with others' findings with dimethylhydrazone lithio anions[4] and the results of studies of related enolate-like species.[8] Theoretical treatments of four-atom, six-electron systems predict that the *Z* isomer should be favored over the *E* isomer.[9] In the case of **4a** we can experimentally determine this stability to be 1.3 kcal/mol based on the predominance of *Z*-**4a** over *E*-**4a** at 35 °C (NMR probe temperature).

When propionaldehyde dimethylhydrazone (**3b**) was deprotonated with excess LDA at room temperature and the resulting solid dissolved by addition of 2.0 equiv of HMPA per lithium atom, the ^{1}H NMR spectrum of **4b** at −12 °C showed one broad doublet at δ 6.2 (J = 12.5 Hz). Less than 5% of other isomeric lithio anions were present since no other identifiable peaks could be seen by NMR. From the magnitude of the coupling constant, the isomer formed under these deprotonation conditions is *E* about the C_1–C_2 bond. The ^{1}H NMR spectrum of **4b** generated in the presence of 2.5 equiv of HMPA/Li shows two doublets at δ 6.2 (J = 12.5 Hz) and 6.6 (J = 7.7 Hz) in a ratio of ca. 15/85. This type of reversal of stereochemistry when HMPA is added to LDA was first reported by Ireland for deprotonation of esters.[10] In our communication we reported slightly lower stereoselectivity for each of these steps, apparently because of incomplete deprotonation in LDA/THF (excess LDA is necessary to ensure that deprotonation is complete before solubilization with HMPA) and because of a ratio of HMPA/Li that was ca. 1.7 instead of 2.5. We also assumed in our communication that both isomers of **4b** had *Z* stereochemistry about the C–N bond.[5] Subsequent trapping experiments with 1-iodobutane show, however, that the major isomers are $E_{C\text{-}C},Z_{C\text{-}N}$-**4b** and $Z_{C\text{-}C},E_{C\text{-}N}$-**4b**.



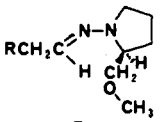
When the mixtures of **4b** generated by these two deprotonation methods were treated with 1-iodobutane (*E*)- and (*Z*)-2-methylhexanal dimethylhydrazone (*E*- and *Z*-**6**) were produced in >87% GC yield. ^{1}H NMR analysis of the product mixtures showed that **6** was formed with an *E*/*Z* ratio of <2:>98 and 87:13 from **4b** generated without HMPA and with 2.5 equiv of HMPA, respectively. These ratios were determined by integration of the formyl proton doublets at δ 6.42 for the *E* and δ 6.73 for the *Z* isomer. The close similarity between the ^{1}H NMR ratios of peaks ascribed to lithio anions with $E_{C\text{-}C}$ and $Z_{C\text{-}C}$ stereochemistry about the C–C bond and $Z_{C\text{-}N}$ and $E_{C\text{-}N}$-**6** obtained by alkylation strongly suggests that the two major lithio anions are $E_{C\text{-}C},Z_{C\text{-}N}$-**4b** and $Z_{C\text{-}C}$, $E_{C\text{-}N}$-**4b**. Space-filling molecular models (CPK) support these assignments. A model of $Z_{C\text{-}C},Z_{C\text{-}N}$-**4b** clearly shows that the methyl group on C-2 will overlap with one methyl group bonded to nitrogen if the three atoms of the π system (C–C–N) remain conjugated and sp^2 hybridized. Presumably electronic factors favoring *Z* stereochemistry about the C–N bond are overwhelmed by the steric interaction of a cisoid alkyl group with the dimethylamino group.

When the phenylacetaldehyde dimethylhydrazone (**3c**) and trimethylsilylacetaldehyde dimethylhydrazone (**3d**) were deprotonated by LDA in the presence or absence of HMPA and the ^{1}H NMR spectra were recorded at 35 °C, only species with *E* configuration about the C_1–C_2 bond were observed. The ^{1}H NMR spectrum of **4c** showed, in addition to peaks from phenyl protons, two doublets at δ 7.3 (J = 12 Hz) and 8.0 (J = 13 Hz) in a ratio of 7:1, respectively. The ^{1}H NMR spectrum of **4d** consisted to two doublets at δ 6.4 (J = 15.6 Hz) and 7.2 (J = 16.4 Hz), in a ratio of 4:1, respectively. In both cases the formyl proton signal from the major species is upfield. Based on our observation that the formyl proton signal from *Z*-**4a** is upfield from the signal from *E*-**4a** and previous results,[6,10] we assign the $E_{C\text{-}C},Z_{C\text{-}N}$ structure to the major isomers of **4c** and **4d** and the $E_{C\text{-}C},E_{C\text{-}N}$ structure to the minor isomers.

Corroboration of the stereochemical assignments for **4c** was obtained by methylation with iodomethane of **4c** generated with LDA in the absence of HMPA. The NMR spectrum of the crude 2-phenylpropanal dimethylhydrazone (ca. 85% yield) arising from this alkylation showed that both the $Z_{C\text{-}N}$ and $E_{C\text{-}N}$ isomers were present in a ratio of 6:1. Over a period of 30 min at 30 °C the signals from the (originally) predominant

Z isomer disappeared as the thermodynamically favored *E* isomer was formed.

Chiral Aldehyde Hydrazones. Our observation that the stereochemistry about the C_1–C_2 bond in **4b** could be controlled by varying deprotonation conditions suggested that we might be able to alter the course of asymmetric electrophilic substitution of chiral aldehyde hydrazone lithio anions by simply modifying the composition of the base solution. Accordingly, we studied two chiral aldehyde hydrazones (**7a,b**) which have been used in successful asymmetric syntheses.[3]



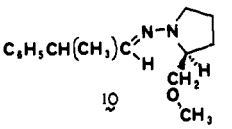
7

a: R = CH_3–
b: R = C_6H_5–

Deprotonation of **7a** with 1.1 equiv of LDA in THF at 0 °C for 7 h gave a solution of anion **8a.** An ^1H NMR spectrum recorded at −16 °C contained a doublet for the formyl proton at δ 5.96 (J = 12.2 Hz) indicating stereoselective (>98%) formation of a lithio anion with *E* stereochemistry about the C_1–C_2 bond. By analogy to other aldehyde hydrazone anions with *E* stereochemistry about C_1–C_2 and by the similarity of the chemical shift for the formyl proton of **8a** to that from $E_{C\text{-}C},Z_{C\text{-}N}$-**4b,** we assign the $E_{C\text{-}C},Z_{C\text{-}N}$ stereochemistry to this lithio anion. When **7a** was deprotonated at −16 °C with 1.1 equiv of LDA in THF containing 2.2 equiv of HMPA, a new species was formed. An ^1H NMR spectrum run at −16 °C showed <5% of $E_{C\text{-}C},Z_{C\text{-}N}$-**8a** and a new doublet at δ 6.64 (J = 7.7 Hz). The stereochemistry about the C_1–C_2 bond in the new species must be *Z*. By analogy to **4b** and the near equivalence of the chemical shifts of $Z_{C\text{-}C},E_{C\text{-}N}$-**4b** and this new species, we assign the $Z_{C\text{-}C},E_{C\text{-}N}$ stereochemistry to the lithio anion formed by deprotonation of **7a** in the presence of HMPA.

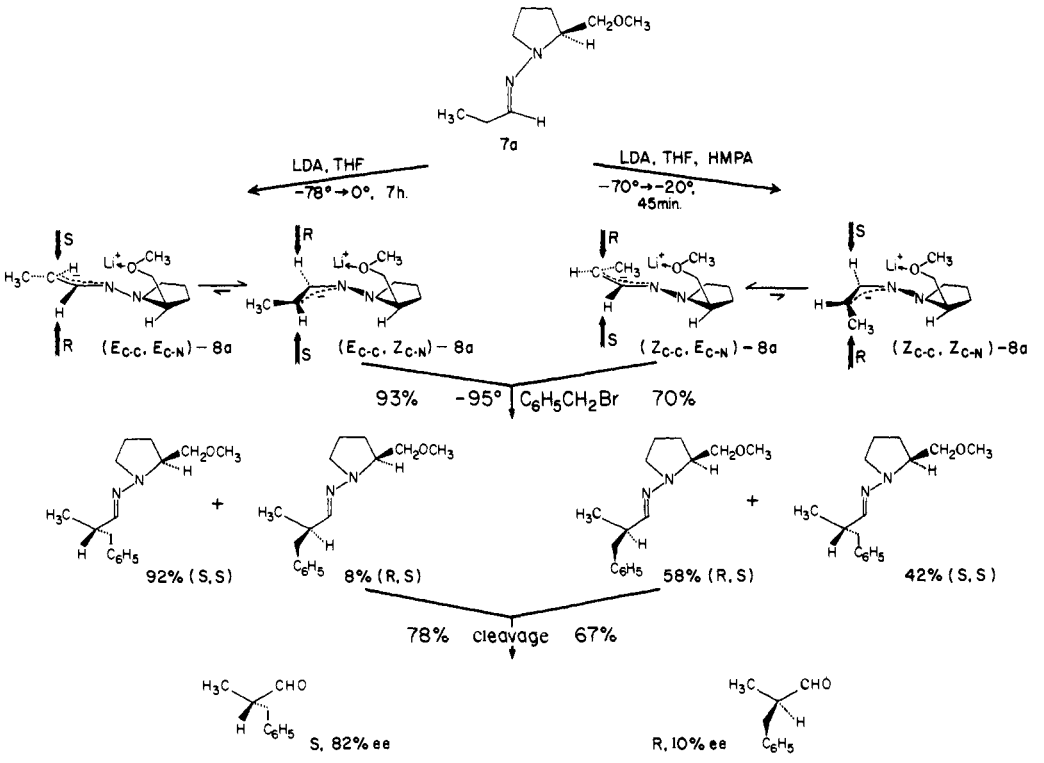
Complete reversal of the stereochemistry about the C_1–C_2 and C–N bonds in **8a** might be expected to have a dramatic effect on the overall stereoselectivity in an alkylation reaction sequence since isomerization about the C_1–C_2, C–N, or N–N bond reverses the prochiral face of the anion which is nearest the methoxy group of the aminomethoxymethylpyrrolidine. When the $E_{C\text{-}C},Z_{C\text{-}N}$-**8a** was produced on a synthetic scale by the above procedure and alkylated at −95 °C with benzyl bromide, we obtained a 93% yield of a mixture of diastereomers with 84% stereoselectivity (^1H NMR spectrum with $Eu(fod)_3$). Cleavage of the C–N hydrazone moiety gave in 78% yield 2-methyl-3-phenylpropanal (**9**) with 82% optical purity (*S* preferred). Alternatively, alkylation of *Z,E*-**8a** under similar conditions gave a 70% yield of diastereomers with a 16% stereoselectivity (the opposite diastereomer to that found above was preferred) which upon cleavage gave a 67% yield of **9** with 10% optical purity (*R* preferred) (Scheme I). For the reactions of hydrazone **7a,** deprotonation with either base system is almost completely stereoselective but the alkylation of $E_{C\text{-}C},Z_{C\text{-}N}$-**8a** or $Z_{C\text{-}C},E_{C\text{-}N}$-**8a** limits the optical yield of the reaction.

When the chiral hydrazone **7b** was deprotonated with LDA in THF at 0 °C, a yellow precipitate formed. Addition of 2.0 equiv of HMPA gave a homogeneous, red solution, the ^1H NMR spectrum recorded at 25 °C of which showed two doublets for the formyl protons at δ 7.2 (J = 12 Hz) and 8.0 (J = 13 Hz) in a ratio of about 10:1, respectively. Based on our results with lithio dimethylhydrazone anion **4c** both species must have *E* stereochemistry about the C–C bond and the upfield doublet is assigned to $E_{C\text{-}C},Z_{C\text{-}N}$-**8b** and the downfield doublet to $E_{C\text{-}C},E_{C\text{-}N}$-**8b.** A similar spectrum was observed for the anion generated from a base solution to which HMPA was added before addition of **7b.** Alkylation of the anion solution with excess iodomethane at −78 °C gave quantitative (NMR, GC) formation of a mixture of diastereomers **10**. Analysis of



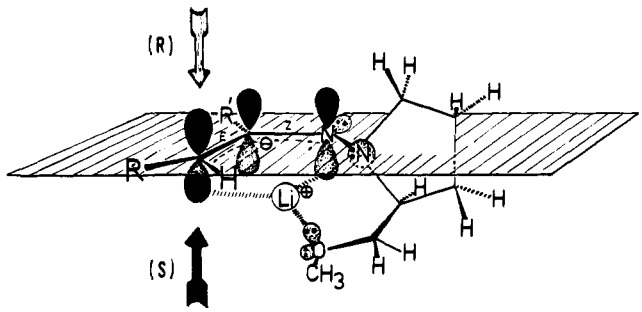
10

Scheme I



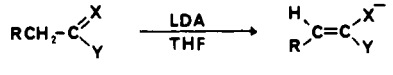
this mixture with the shift reagent $Eu(fod)_3$ showed 66% diastereomeric excess. Previously we reported 31% stereoselectivity (*R* preferred) for the synthesis of 2-phenylpropanal via the anion of the chiral hydrazone **7b**.[3c] This lower stereoselectivity reported previously probably reflects racemization occurring in the hydrolysis of the product hydrazone. At −78 °C, anion **8b** should be >95% $E_{C\text{-}C},Z_{C\text{-}N}$,[11] and we can set limits on the stereoselectivity in each step of this asymmetric synthesis. Deprotonation at 0 °C occurs with >98% stereoselectivity to give the *E* stereochemistry about the C-C bond. Alkylation of $E_{C\text{-}C},Z_{C\text{-}N}$-**8b** with iodomethane at −78 °C occurs with about 66% stereoselectivity. This represents an energy difference of only 0.6 kcal/mol for the diastereomeric transition states for this electrophilic substitution vs. greater than 2 kcal/mol difference between the diastereomeric transition states in the deprotonation reaction if we are observing kinetic products of deprotonation.

Although the drawings of **8a** in Scheme I shows specific conformations about the N-N bond (and consequently a specific position for coordinated lithium), we have no experimental data favoring any single N-N conformation. This present lack of structural data prevents us from making firm predictions about the N-N geometry. Nonetheless, molecular models (CPK) do suggest that large steric differences between the diastereotopic faces of N-N conformers of $Z_{C\text{-}N}$ species exist while smaller steric differences are seen between the diastereotopic faces of N-N conformations of $E_{C\text{-}N}$ species. Changes in N-N conformation have a significant effect on the details of electrophilic substitution of these chiral lithio anions since for some N-N conformations the major observed product would have to be rationalized by electrophilic substitution syn to lithium while other possible N-N conformations would necessitate an electrophilic substitution anti to coordinated lithium. For example, a drawing of $E_{C\text{-}C},Z_{C\text{-}N}$-**8a** showing a perpendicular pyrrolidine ring requires that electrophilic substitution occur mainly syn to a coordinated lithium to explain the major product's *S* configuration at the new chiral center in contrast to the anti attack suggested by the analogous drawing of Scheme I. Unresolved questions about the direction of electrophilic substitution (relative to lithium) also exist in other electrophilic asymmetric synthesis.[12]

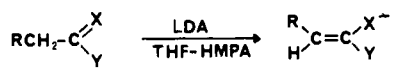


Discussion

Deprotonation of monosubstituted acetaldehyde hydrazones with LDA in THF is shown in this work to always lead to anionic species which are predominantly *E* about the C_1-C_2 bond. Furthermore, this is known to be a general case for LDA deprotonations of monosubstituted carbonyl compounds and their derivatives (eq 1). For example, stereoselectivity like that



(1)

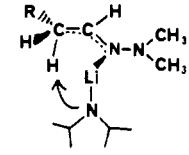


(2)

shown in eq 1 is observed in LDA/THF deprotonation of oxazolines,[12] esters,[10] aldehydes,[13] ketones,[10,14] and thioamides.[15] Severe steric hindrance to formation of *E* ketone enolates explains exceptions to this generalization noted by Heathcock.[14a] Our observation that the presence of HMPA in LDA solutions leads to a reversal of stereoselectivity in deprotonation of propionaldehyde hydrazones is precedented by the results obtained by Ireland for ester deprotonations[10] and by Heathcock[14a] and Kuwajima[14c] for ketone deprotonations (eq 1). We and Meyers have also independently observed similar trends in the stereoselectivity of oxazoline deprotonation in the presence of THF/HMPA, although a reversal of stereoselectivity was not observed in this case.[12]

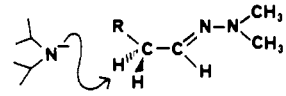
The fact that the generalizations regarding stereoselectivity represented by eq 1 and 2 for deprotonations by LDA in the presence or absence of HMPA appear to hold for diverse active methylene compounds suggests to us that any rationalization of these results should focus on the different nature of LDA in THF vs. LDA in THF/HMPA. An alternative rationalization of these results first suggested by Ireland for ester deprotonations was based on the steric bulk of an -OLi group vs. an $-O^-$ group and the steric interactions of these groups with the alkyl substituent on the α carbon.[12] Such an explanation is, however, not general since it requires that charged nitrogen behave as if it were smaller than a formyl proton in the case of the LDA/HMPA/THF deprotonations of aldehyde hydrazones.

We prefer to interpret our results and others cited above in slightly different terms. Specifically, we believe that different transition states obtain for deprotonation in the presence or absence of HMPA. When no HMPA is present, a *closed* transition state like A (which resembles Ireland's model) might be expected for steric reasons.



A

When HMPA is added to the LDA solution before deprotonation, solvation of the lithium ion by the HMPA undoubtedly occurs. In this case, we envision an *open* transition state such as B. Thus we relate the predominant formation of



B

Z product in LDA/THF/HMPA deprotonations to the well-known preference for eclipsed conformations of substituted carbonyl compounds in solution.[16]

If the model of an "open" transition state for deprotonation in the presence of HMPA is correct, one would expect that, when a bulky R group is present at the α carbon, steric interaction between the hydrazone nitrogen and the R group would dominate and *E* lithio anions would be formed. Such a rationalization might explain why the α-phenyl and α-trimethylsilyl hydrazones **3c** and **3d** give *E* lithio anions even when HMPA is present during the deprotonations. However, we have not yet been able to rule out the possibility that we observe the thermodynamic products for equilibration processes which occur in these cases before the ^1H NMR spectra are run. Equilibration could occur via a protonation-deprotonation sequence or via a rotational process. The recent observation by Meyers that metallo enamines prepared by deprotonation

with LDA can equilibrate in refluxing THF[17] could be explained by such a protonation–deprotonation sequence or by C–C bond rotation.

Deprotonation of chiral hydrazone **7a** was found to have stereoselectivity comparable to that observed in deprotonation of the achiral analogue **3b** in both the LDA and LDA/HMPA bases systems. However, the results of the alkylations of chiral lithio hydrazone anions E_{C-C},Z_{C-N}-**8a**, Z_{C-C},E_{C-N}-**8a**, and the mixture of E_{C-C},Z_{C-N}-**8b** and E_{C-C},E_{C-N}-**8b** clearly indicate that the alkylation reactions are less stereoselective than the deprotonation reactions which form these species. This has also been found to be the case for the formation of chiral oxazoline anions with LDA and subsequent alkylations of these species.[12] This conclusion suggests that even more successful asymmetric syntheses employing chiral hydrazones might be possible if more selective alkylation reagents or conditions were used.

Conclusion

In conclusion, we have found that the stereochemistry of lithio aldehyde hydrazone anions can be determined readily by ^{1}H NMR spectroscopy and can be related to subsequent alkylation studies. In selected cases, deprotonation of aldehyde hydrazones with LDA or LDA/HMPA was found to give a reversal in the major isomer of lithio anion formed which can be explained in terms of dramatically different transition states for deprotonation under these conditions. By changing conditions of a chiral hydrazone deprotonation, we have effected the reversal of the sense of an asymmetric synthesis from one chiral precursor. Such techniques should be useful in further developing rational asymmetric syntheses which employ naturally occurring or synthetic chiral auxiliaries to induce asymmetry in electrophilic substitution reactions.

Experimental Section

All reactions of organometallic species were run under nitrogen and employed unexceptional inert-atmosphere techniques including syringe transfers. Diisopropylamine was distilled from calcium hydride and stored over 4A molecular sieves. Tetrahydrofuran (THF) was distilled from sodium–benzophenone dianion immediately prior to use. Hexamethylphosphoramide (HMPA) was distilled in vacuo from sodium and stored over 4A molecular sieves. ^{1}H NMR spectra were recorded on Varian T-60, FT-80, HA-100, and A-60 spectrometers. Benzene-d_6 was used for an internal deuterium lock for FT-80 spectra.

Aldehyde dimethylhydrazones 3a, 3b, and 3c were prepared by allowing the appropriate aldehyde (Aldrich) to react with 1 equiv of *unsym*-dimethylhydrazine (Aldrich) at 0 or 25 °C. Distillation gave the desired hydrazones in high yield which were >95% pure by ^{1}H NMR.

(*E*)- and (*Z*)-Trimethylsilylacetaldehyde Dimethylhydrazone (3d). A solution of 5 mL of THF, 8.6 mL of 1.48 M *n*-butyllithium (Aldrich, *n*-BuLi, 12.8 mmol), and 1.8 mL of diisopropylamine (12.8 mmol) at −78 °C was stirred for 30 min and allowed to warm to 25 °C. The solution was cooled to −78 °C and 1.25 mL (ca. 11.6 mmol) of **3a** was added. The mixture was stirred at −78 °C for 30 min and 0 °C for 90 min. The mixture was cooled to −78 °C and 1.65 mL (13 mmol) of chlorotrimethylsilane (Aldrich, redistilled) was added. After 20 min the mixture was warmed to 0 °C, and stirring was continued for 30 min. The reaction mixture was poured into 75 mL of aqueous 5% sodium carbonate solution and extracted twice with 25-mL portions of ether. The combined ether fractions were washed with water and saturated aqueous sodium chloride and dried (magnesium sulfate). Distillation of the solvent at reduced pressure gave crude *E*- and *Z*-**3d** in an 89:11 ratio which was determined by ^{1}H NMR. Signals from the major *Z* isomer occurred at δ 6.8 (t, J = 7 Hz), 2.3 (s), and 1.9 (d, J = 7 Hz); those from the minor *E* isomer occurred at δ 6.5 (t, J = 6 Hz), 2.5 (s), and 1.6 (d, J = 6 Hz). A sample of **3d** purified by preparative gas chromatography (0.25 in. by 6 ft 10% SE-30 on 60/80 Chromosorb W at 130 °C) contained only *E*-**3d** by ^{1}H NMR analysis.

A reaction similar to that described above using 37 mmol of **3a** gave crude **3d** which was distilled (bp 153–155 °C; lit.[2] bp 97 °C, 75 Torr) to give a 59% yield of *E*-**3d** which was >95% pure by analytical GC and ^{1}H NMR.

Alkylation of Lithio Dimethylhydrazone Anions. The following general procedures were used. An LDA solution made from *n*-butyllithium in hexane and an equivalent amount of diisopropylamine in THF containing 2.0 equiv of HMPA per lithium ion if desired was cooled to −78 °C. To this solution was added the appropriate DMH (**3a**, **3b**, or **3c**). The resulting mixture was stirred at −78 °C for 15–30 min and then allowed to warm at the desired deprotonation temperature for 30–45 min. The mixture was then cooled to −78 °C and 1.0–1.2 equiv of 1-iodobutane or iodomethane was added. After stirring at the desired alkylation temperature for 30 min, this reaction mixture was quenched with water or 10% aqueous ammonium chloride solution. In those reactions in which the *E*/*Z* ratio of hydrazone products was determined by ^{1}H NMR, the products were isolated in 69–85% yield after addition of ether and extraction of the organic phase with aqueous sodium bicarbonate and aqueous sodium chloride solutions, drying (Na_2SO_4), and removal of the solvent at 1 Torr and 0 °C. Alternatively, extraction of the aqueous washes three times with ether and combination of the organic phases typically gave yields of greater than 90% by GC comparison to an internal standard. Because of the partial solubility of DMH products **5** and **6** in THF/water, the latter procedure is preferred in synthetic experiments.

(*E*)- and (*Z*)-Hexanal Dimethylhydrazone (5). A. A base solution was prepared from 0.72 mL (5.1 mmol) of diisopropylamine and 3.8 mL of 1.35 M *n*-butyllithium (5.1 mmol) in 5 mL of THF. Deprotonation of 0.54 mL (5.0 mmol) of **3a** by the general procedure at −23 °C followed by alkylation with 0.59 mL (5.1 mmol) of 1-iodobutane at −23 °C gave a 69% isolated yield of **5** which consisted of *E*- and *Z*-**5** in a 10/90 ratio (integration of signals at δ 6.61 and 6.96, respectively).

B. In a reaction identical with A with the exceptions that 1.75 mL (10.1 mmol) of HMPA was added to the lithio anion solution before alkylation and the alkylation temperature was −78 °C, a 71% yield of *E*- and *Z*-**5** in a ratio of 11/89 was isolated.

(*E*)- and (*Z*)-2-Methylhexanal Dimethylhydrazone (6). C. A base solution was prepared from 1.05 mL (7.5 mmol) of diisopropylamine and 4.9 mL of 1.52 M *n*-butyllithium (7.5 mmol) in 5 mL of THF. Deprotonation of 0.5 g (5 mmol) of **3b** by the general procedure at 25 °C for 45 min followed by cooling to −78 °C, addition of 3.2 mL (19 mmol) of HMPA, and alkylation with 0.9 mL (7.8 mmol) of 1-iodobutane at −78 °C gave a mixture of *E*- and *Z*-**6** in a ratio of <2/>98, respectively, as determined by ^{1}H NMR integration of the formyl proton doublets at δ 6.42 (*E*) and 6.73 (*Z*). Back-extraction of the aqueous washings as described above and GC analysis indicated a 90% yield of **6** by comparison to an internal standard of tetradecane.

D. Reaction C above was repeated with the exceptions that the HMPA was added to the base solution before **3b** was added and the deprotonation was run at −23 °C for 30 min. After workup, an 81% yield of *E*- and *Z*-**6** in the ratio of 87/13, respectively, was obtained.

2-Phenylpropanal Dimethylhydrazone. A base solution was prepared from 1.0 mL (7.1 mmol) of diisopropylamine and 4.5 mL of 1.5 M *n*-butyllithium (6.75 mmol) in 5 mL of THF. Deprotonation of 1.0 g (6.2 mmol) of **3c** by the general procedure at 25 °C for 9 h followed by alkylation with 0.5 mL (7.5 mmol) of iodomethane at 0 °C gave crude 2-phenylpropanal dimethylhydrazone (80–85%) which was pure by ^{1}H NMR. The ^{1}H NMR spectrum of neat product taken within 5 min of warming to 30 °C contained the *Z* and *E* isomers in a 6:1 ratio, respectively. Over a period of 30 min at 30 °C the product isomerized cleanly to the *E* isomer. ^{1}H NMR spectrum of the *E* isomer (neat, relative to external Me_4Si in $CDCl_3$): δ 6.77 (s, 5 H), 6.15 (d, 1 H, J = 5.5 Hz), 3.16 (m, 1 H), 2.13 (s, 6 H), 0.93 (d, 3 H, J = 7 Hz). ^{1}H NMR spectrum of the *Z* isomer (neat, relative to external Me_4Si in $CDCl_3$): δ 6.7 (s), 6.5 (d, partially hidden), 4.01 (m), 1.93 (s), 0.76 (d, J = 7 Hz).

(*S*)-1-Amino-2-methoxymethylpyrrolidine (SAMP) was made from L-proline by sequential $LiAlH_4$ reduction, nitrosation, methylation, and $LiAlH_4$ reduction as described previously.[3b]

Chiral aldehyde hydrazones **7a** and **7b** were prepared from the corresponding aldehydes and SAMP as previously described.[3c]

(*S*)-2-Methyl-3-phenylpropanal ((*S*)-9). A mixture of 6.5 mL of THF and 2.6 mL of diisopropylamine was cooled to −78 °C and treated with 8.45 mL of 1.69 M *n*-butyllithium (14.3 mmol). After stirring for 30 min at −78 °C, 2.21 g (13 mmol) of **7a** in 6.5 mL of THF was

added. The mixture was allowed to warm to 0 °C and was stirred for 7 h. The resulting mixture was cooled to −95 °C and treated with 1.71 mL (14.3 mmol) of benzyl bromide in 3 mL of THF. The reaction mixture was kept at −95 to −90 °C for 1 h, and was then allowed to warm to 0 °C. An extractive workup with methylene chloride and water followed by drying (sodium sulfate) and removal of the solvent under reduced pressure gave ca. 100% yield of crude product which was distilled to give 3.15 g (93%) of a colorless oil, bp 150–160 °C (0.2 Torr), $[\alpha]^{22}_D$ −56° (neat). Analysis of the product by ^{1}H NMR using the shift reagent Eu(fod)$_3$ indicated a 92:8 ratio of diastereomeric products. The product hydrazone (1.3 g, 5 mmol) was treated with 5 mL of iodomethane, and the mixture was heated at 60 °C for 14 h. Excess iodomethane was removed in vacuo and the hydrazonium iodide was treated with 30 mL of 3 N HCl and 40 mL of pentane. The resulting mixture was stirred for 20 min at 25 °C. The organic phase was washed twice with water and dried (sodium sulfate). Removal of the solvent and distillation afforded 0.58 g (78%) of (*S*)-**9** as a colorless oil, bp 80–100 °C (2 Torr), with 82% optical purity, $[\alpha]^{20}_D$ +4° (*c* 1.25, acetone).[3c]

(*R*)-2-Methyl-3-phenylpropanal ((*R*)-9). To an LDA mixture at −78 °C prepared as described above was added 6.5 mL of HMPA. The mixture was warmed to 0 °C and stirred until it became homogeneous. The solution was cooled to −78 °C and 2.21 g (13 mmol) of **7a** in 6.5 mL of THF was added dropwise. The resulting yellow suspension was stirred for 30 min and warmed to −20 °C for 15 min to give a clear solution. This solution was cooled to −95 °C and treated as above with 1.71 mL (14.3 mmol) of benzyl bromide. The mixture was stirred for 1 h at −95 to −90 °C and then was warmed to −60 °C. Workup as above afforded 2.64 g (79%) of crude product hydrazone which was distilled to give 2.35 g (70%) of a colorless oil, bp 145–160 °C (0.2 Torr), $[\alpha]^{22}_D$ −80° (neat). ^{1}H NMR analysis of this product using Eu(fod)$_3$ indicated a 58:42 ratio of diastereomeric products (the diastereomer in excess was the minor diastereomer from the previous experiment described above). Cleavage of 1.3 g (5 mmol) of the product hydrazone by the procedure described above gave 0.5 g (67%) of (*R*)-**9** as a colorless oil, bp 80–100 °C (2 Torr), with 10% optical purity, $[\alpha]^{22}_D$ −0.5° (*c* 1.9, acetone).

Reaction of 8b with Iodomethane. To a LDA solution made from 1.25 mL of THF, 0.35 mL of diisopropylamine, and 1.5 mL of 1.5 M *n*-butyllithium (2.2 mmol) in hexane at −78 °C was added 490 mg (2.1 mmol) of hydrazone **7b** in 0.5 mL of THF. The resulting mixture was warmed to 0 °C and stirred for 1.5 h; a yellow precipitate formed. Addition of 1 mL of HMPA at 0 °C gave a deep red solution which was suitable for ^{1}H NMR analysis. The reaction mixture was then alkylated with iodomethane at −78 °C, allowed to warm slowly to 25 °C over several hours, and finally stirred at 25 °C for 8 h. After addition of water and ether, the product was isolated by an extractive workup. GC analysis (SE-52 or Carbowax 20M) indicated quantitative conversion to the methylated product. Crude product isolated by distillation of the solvent in vacuo was analyzed by ^{1}H NMR with the shift reagent Eu(fod)$_3$. The broad singlets from the formyl protons and the doublets from the methyl protons of the diastereomeric hydrazones were resolved. Integration of these peaks indicated that the diastereomeric ratio was 83:17 (±2).

NMR Studies of Aldehyde Hydrazone Lithio Anions. Samples were prepared by addition of the appropriate hydrazone to excess LDA in THF in the presence of 0.0 or 2.2–2.5 equiv of HMPA per lithium ion at −78 °C followed by warming to −20 to 25 °C depending on the hydrazone used. When no HMPA was present, lithio anions **4a, 4b, 4c, 4d,** and **8b** (but not **8a**) precipitated from solution, and the reaction mixture was subsequently treated with 2 equiv of HMPA per lithium ion at −78 °C to effect solution. Representative deprotonation conditions used for **7a** are given below.

A. A solution of 0.5 mL of THF and 0.2 mL of diisopropylamine was cooled to −78 °C, and 0.8 mL of 1.4 M *n*-butyllithium (1.1 mmol) was added (in the case of insoluble lithio anions such as **4b** 1.5 equiv of LDA was typically used). After stirring for 30 min at −78 °C, a solution of 170 mg (1 mmol) of **7a** in 0.5 mL of THF was added. The mixture was stirred and allowed to warm to 0 °C. After 7 h at 0 °C, 1 mL of the solution was transferred to a dry NMR tube at 0 °C, 50 μL of benzene-d_6 was added, and the spectrum was recorded at −16 °C.

B. An LDA solution identical with that described in A above was prepared. To this solution was added 0.5 mL of HMPA at −78 °C. The mixture was warmed to 0 °C, stirred until it became homogeneous, and then cooled to −78 °C. A solution of 170 mg (1 mmol) of **7a** in 0.5 mL of THF was added and the resulting mixture was stirred at −78 °C for 30 min. One milliliter of the reaction mixture was transferred to an NMR tube which was maintained at −78 °C (we believe that the solution never warmed above −20 °C during this transfer). Benzene-d_6 (50 μL) was added to the NMR tube and the ^{1}H NMR spectrum was recorded at −16 °C.

^{1}H NMR spectra of lithio anions **4a, 4c, 4d,** and **8b** were recorded at 35 °C. Spectra of lithio anions **4b** and **8a** were recorded at −10 to −20 °C. When either **4b** or **8a** in the presence of HMPA was allowed to warm to 35 °C in the probe of an NMR spectrometer, the signals arising from the formyl protons were lost within 10–30 min.

Acknowledgments. We are grateful to the Robert A. Welch Foundation and the Deutsche Forschungsgemeinschaft for support of this work. Funds for the Varian FT-80 NMR spectrometer used in this work were provided, in part, by a National Science Foundation grant to Texas A&M University (CHE77-09279).

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