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N-Aminoaziridinylhydrazones: Highly Diastereoselective Alkylation without Chelation, and a Syn-Directing Effect

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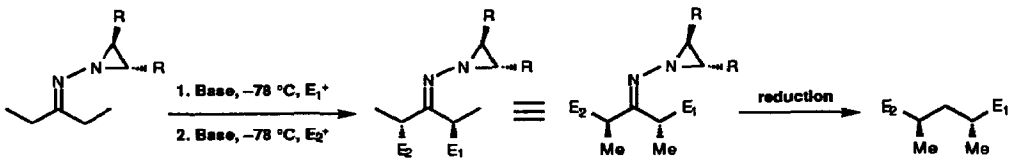
Abstract: The alkylation of C_2-symmetric N-aminoaziridinylhydrazone anions shows excellent diastereoselectivity despite the absence of chelating groups in the chiral auxiliary. In contrast to other dialkylhydrazones, aziridinylhydrazones exhibit a syn-directing effect analogous to that observed for arenesulfonylhydrazones.

Deoxypolypropionates consisting of alternating monomethylated and unsubstituted methylene groups are commonly found in polyketide natural products.[1] We sought to develop a highly convergent strategy for the synthesis of such chains that would allow bidirectional elongation[2] via sequential α, α' alkylations of a ketone derivative, followed by direct conversion into the hydrocarbon. A chiral hydrazone could in principle serve this purpose if one could be identified that behaves like a SAMP or RAMP derivative[3] with respect to the alkylation diastereoselectivity, but like an arenesulfonylhydrazone towards reducing agents, i.e., reductive elimination to give the hydrocarbon[4] rather than addition/hydrogenolysis to give the amine.[3] We anticipated that chiral hydrazones derived from 2,3-trans disubstituted N-aminoaziridines (Figure 1) might well serve this dual role, based on their structural similarity to SAMP/RAMP hydrazones in conjuction with several precedents for elimination reactions reminiscent of arenesulfonylhydrazones.[5] We earlier reported that such hydrazones are indeed reduced as predicted, and under unusually mild conditions ($LiAlH_4$, room temperature).[6] In the interim, Enders has achieved the sequential α, α'-alkylation of a SAMP hydrazone,[7] prompting us to describe our studies on the alkylation of N-aminoaziridinylhydrazones. Although the most effective auxiliary found thus far (R = isopropyl) has resisted our efforts to prepare it in enantiomerically pure form, it is noteworthy that azaenolates derived from this N-aminoaziridinylhydrazone undergo α-alkylation with very high diastereoselectivity despite the absence of a chelating group in the auxiliary. In addition, their chemistry has proven to be interesting and quite atypical of "normal" dialkylhydrazones, and we report our preliminary findings in this Letter.

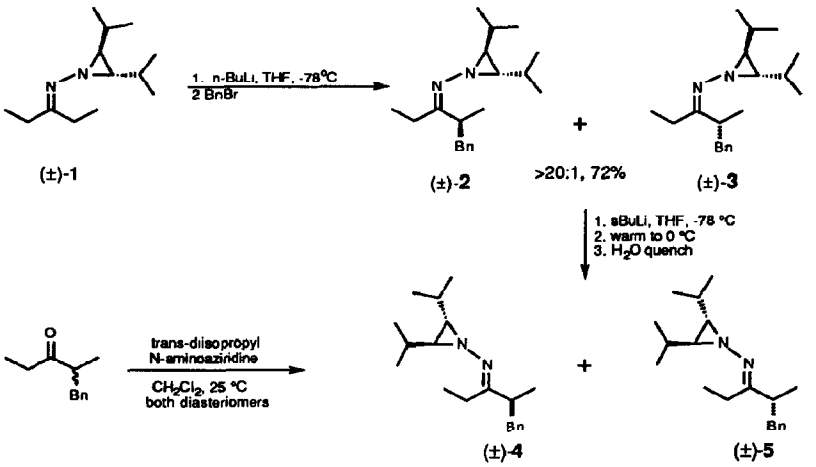
Figure 1



Initial studies focused on the preparation of hydrazones derived from C_2-symmetric disubstituted N-aminoaziridines, which to our knowledge had not previously been prepared in enantiomerically pure form. Several trans-disubstituted N-aminoaziridinylhydrazones with chelating methoxymethyl groups analogous to

SAMP were readily prepared from tartaric acid, but the derived anions decomposed under low temperature alkylation conditions, apparently through vinylogous β-elimination of a methoxy group with concommittant aziridine ring opening.[8] At that point, molecular modeling indicated that SAMP-like chelation might in fact not be necessary if sufficiently bulky alkyl groups were present on the aziridine ring. Indeed, alkylations of several simple tartrate-derived dialkyl N-aminoaziridinylhydrazones (R = n-hexyl, benzyl, and cyclohexylmethyl) proceeded with moderate selectivity, giving diastereomeric excesses on the order of 70%[9] and providing some reassurance of the validity of the modeling studies. Unfortunately, all attempts to prepare more hindered dialkyl derivatives with α-branching (e.g., R = isopropyl) failed. Thus, in order to investigate the diastereoselectivity of alkylation in these more highly branched derivatives we resorted to racemic 2,3-trans diisopropyl N-aminoaziridine, which was readily prepared via modification of literature procedures, and which was easily converted into the corresponding hydrazones.[5b] Deprotonation of 3-pentanone *trans*-2,3-diisopropyl-1-aminoaziridine hydrazone **1** with n-BuLi in THF at -78 °C produced a stable azaenolate, the alkylation of which with benzyl bromide produced **2** *as a single detectable diastereomer* in 72% yield (Scheme 1). The sense of induction shown in Scheme 1 is based on an analogous alkylation of the enantiomerically pure 2R,3R-dicyclohexylmethyl N-aminoaziridinylhydrazone followed by hydrolysis and comparison with the corresponding authentic enantiomerically enriched ketone.[9] This relative stereochemistry is also consistent with our preliminary modeling studies, but must be considered tentative since it is based on analogy rather than direct evidence. Nonetheless, the alkylation of **1** is remarkably stereoselective, especially considering the absence of chelating groups in the auxilary.

Scheme 1. Alkylation Studies of trans Diisopropyl N-Aminoaziridine Hydrazones

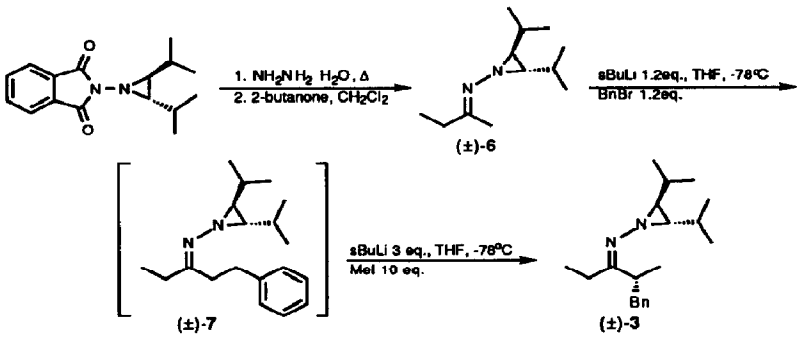


In order to confirm the structure of **2**, and the absence of the minor diastereomer, an authentic sample containing a 1:1 mixture of **4** and **5** was prepared by condensing the racemic trans-diisopropyl N-aminoaziridine with racemic 2-benzyl-3-pentanone (Scheme 1). This procedure gives the E-configurational isomer of the hydrazone, which was expected from the alkylation reaction, since isomerization of the azomethine bond to the less crowded E-isomer is a facile process that cannot normally be avoided in dialkylhydrazones. To our surprise, however, neither **4** nor **5** corresponded to the alkylation product from **1**,

suggesting that the initially formed alkylated Z-hydrazone had not equilibrated to the more stable E-isomer even after chromatographic purification on silica gel. Confirming this hypothesis, the intially formed alkylation product from **1** was converted into one of the authentic isomers (**4** or **5**) by deprotonation, warming to 0 °C, and quenching with water. This result clearly shows that the initial alkylation product is the Z isomer **2**, which does not spontaneously isomerize to the E isomer during purification. Support for these E/Z assignments is also provided by NMR studies.[10]

The minor alkylation diastereomer **3** also could in principle be prepared by methylation of an unsymmetrical hydrazone (Scheme 2), assuming that the sense of induction for this alkylation is the same as for the aforementioned benzylation. The success of this plan, however, hinges upon the selective formation of the Z-isomer of the hydrazone **7** and its deprotonation syn to the azomethine substituent. There is good precedent for such a "syn-directing" effect in arenesulfonylhydrazones,[11] but it has been shown to be completely absent in "normal" dialkylhydrazones.[12] Because aziridinylhydrazones exhibit reactions more characteristic of the former than the latter, we suspected that despite being diakylhydrazones they would show the syn directing effect characteristic of arenesulfonylhydrazones. Accordingly, 2-butanone hydrazone **6** (Scheme 2) was deprotonated with sBuLi and alkylated with benzyl bromide to give the intermediate hydrazone **7**, the Z-stereochemistry of which was verified by NMR of an aliquot removed from the reaction mixture. In situ deprotonation of **7** with more sBuLi at –78 °C followed by the addition of methyl iodide gave a product identical with **3** in 82% yield. This result clearly implicates a syn directing effect for this hydrazone.

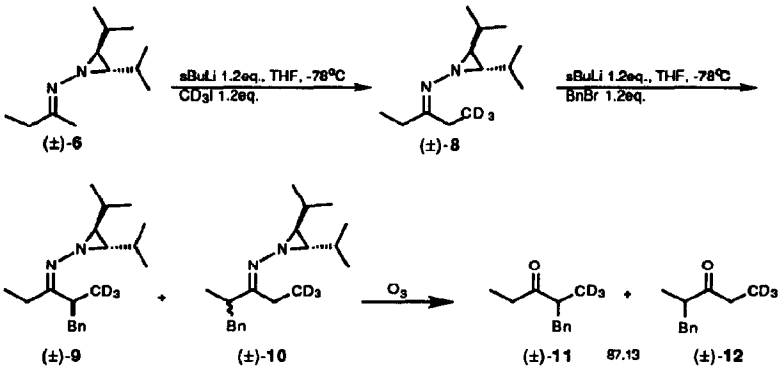
Scheme 2. Evidence of a Syn-Directing Effect



To rule out the remote possibility that the phenyl group strongly influences the deprotonation regioselectivity of **7**, we conducted an experiment that parallels those[12d] that rule out syn deprotonation for other dialkyl hydrazones. Specifically, the hydrazone **6**, (carefully purified by HPLC and determined to be 98% Z by NMR spectroscopy) was deprotonated and then alkylated with CD_3I to give **8** (Scheme 3). This chemically symmetrical hydrazone was isolated and the auxiliary was determined to be > 95% syn to the deuterium label by NMR spectroscopy. The labeled hydrazone (**8**) then was deprotonated with sBuLi in THF at -78°C and alkylated with benzyl bromide to give a mixture of **9** and **10**. The NMR spectrum of the mixture of **9** and **10** was complicated even at 500 MHz, so the hydrazone was cleaved by ozonolysis[3] in order to simplify the analysis. Examination of the mixture of resultant ketones by NMR revealed an 87:13 of **11**:**12**, respectively. We then repeated the identical experiment but with N,N-dimethylhydrazones, which gave a 1:1

mixture of the ketones **11** and **12** (as did the original published experiments with N,N-dimethylhydrazones,[12d] which were carried out under somewhat different reaction conditions). We therefore conclude that in contrast to normal dialkylhydrazones, and despite their stuctural similarity, aziridinylhydrazones do exhibit a moderate syn directing effect. This characteristic would confer a significant element of synthetic versatility not available in other dialkylhydrazones, so that the search for an acceptable route to enantiomerically pure branched 2,3-dialkylaziridinylhydrazones continues.

Scheme 3. Deuterium Isotope Syn Directing Experiments



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