Directed Asymmetric Induction on Aziridinyl Ketones

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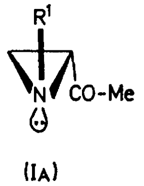
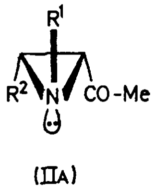
Summary The nitrogen configuration induces the stereochemistry of the addition of hydride (or of an organometallic reagent) to aziridinyl ketones; this phenomenon is interpreted and allows a stereodirected synthesis to be envisaged.

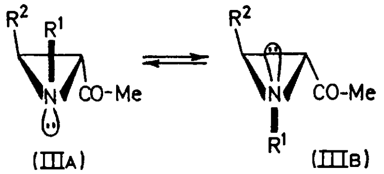
We have shown that β-unsubstituted (I) or β-*cis*-substituted (II) aziridinyl methyl ketones, lead to a single alcohol (in >95% ratio) by kinetic reduction with $LiAlH_4$. The other diastereoisomeric alcohol is obtained stereospecifically by the reaction of MeLi on the required aldehyde. On the other hand, β-*trans*-substituted ketones (III) lead to a diastereoisomeric mixture of the corresponding alcohols. This latter reaction is selective, with the stereoselectivity being temperature dependent. Moreover, in every case, ketones (I) and (II) react more easily than ketones (III). We have shown[1] that the configurations of ketones (I), (II), and (III) correspond to (IA), (IIA), and (IIIA) $\rightleftarrows$ (IIIB), (IIIB) being greatly predominant if R^2 = Buᵗ).†



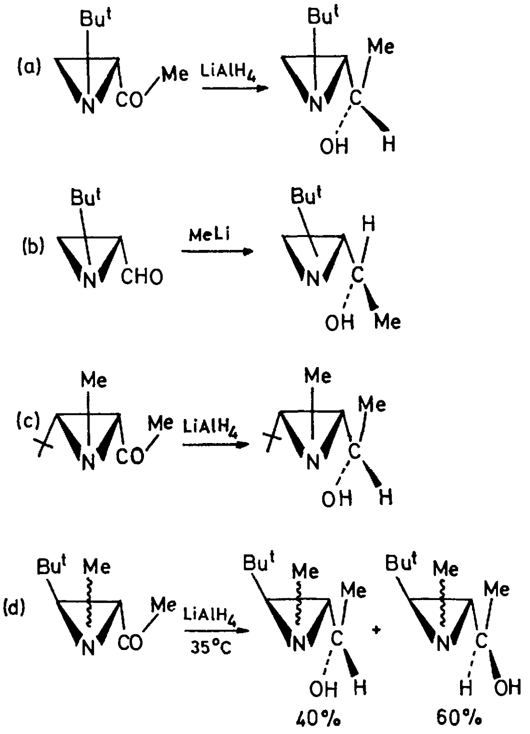
(IA)



(IIA)



(IIIA) (IIIB)



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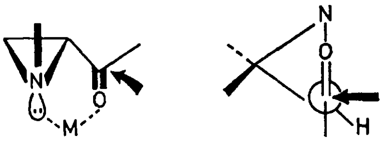
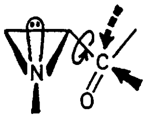
† The configurations (IA), (IIA), (IIIA, B) refer to relationships of substituents with respect to the ring. In the case of (I) and (II), only (IA) and (IIA) are populated and nitrogen inversion is not observed. All the reactions were carried out on enantiomeric pairs.

The configurations of the diastereoisomeric alcohols obtained with $LiAlH_4$ were determined by the method of Deyrup and Moyer[2] (stereospecific formation of oxathiazolidine). Typical examples are shown in (a)—(d).

In the case of (a), (b), and (c), a single product is obtained from −75 to +35 °C; for (d), the selectivity is raised at lower temperatures. The stereochemistry of the reaction is directed by the relative configurations of the nitrogen lone pair and the carbonyl group:



Configuration-A-: stereospecific attack with rigid model



Configuration-B-: two attacks depending on carbonyl conformation

—if they are in a *cis*-relationship [(IA), (IIA), (IIIA), aldehyde of example (b)] the rigid model[3] must be used and the attack takes place stereospecifically on the less hindered side;

—if they are in a *trans*-relationship, (IIIB), the rigid model cannot be used. The use of either the open chain, the Karabatsos, or the Felkin model,[3] on a conformationally labile carbonyl group, leads to a reaction which is only stereoselective. A part of the reagent is complexed by the lone pair and thus explains the lower reactivity.

We observed the same phenomenon for the reaction of aziridinyl methyl ketones (I), (II), and (III), with organometallic reagents (R^3MgX or R^3Li with $R^3 \neq Me$); similar but uninterpreted results were reported by Cromwell *et al.* in 1951,[4] concerning the reactions of aryl aroyl ethyleneimine ketones with organometallic reagents.

Our interpretation of the observed phenomenon allows a stereodirected synthesis of aziridinyl alcohols to be envisaged.

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[1] J. L. Pierre, P. Baret, and P. Arnaud, *Bull. Soc. chim. France*, 1971, **3619** and unpublished results.

[2] J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, 1970, **35**, 3424.

[3] S. I. Yamada and K. Koga in 'Stereoselective Organic Transformations,' Wiley–Interscience, 1970, p. 1.

[4] N. H. Cromwell, J. H. Anglin, F. W. Olsen, and N. G. Barker, *J. Amer. Chem. Soc.*, 1951, **73**, 2803.