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STEREOCONTROL IN ALDOL CONDENSATIONS. THE ROLE OF SOLVENT AND CATION IN THE CONDENSATION OF ACETALDEHYDE WITH THE ANION DERIVED FROM BENZYL 6,6-DIBROMOPENICILLANATE.

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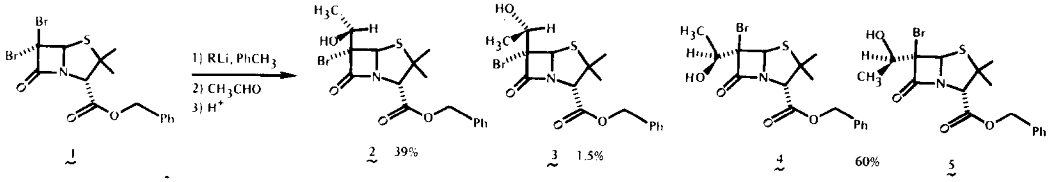
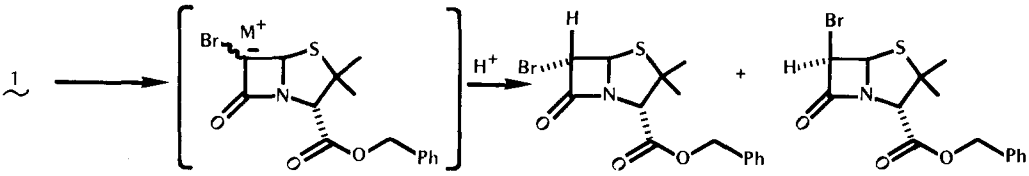
Summary: Unique stereocontrol in aldolization at C6 of penicillanates through modification of solvent and cation has been observed.

Recent discoveries of potent β-lactam antibiotics lacking the usual amido side chain at C-6 and possessing instead a hydroxyalkyl moiety[1] have stimulated the development of methods for obtaining the corresponding hydroxyalkyl penicillanates. Chemists at Merck have reported a successful synthetic method[2] exploiting an earlier observation made by Clayton[3] during his investigations into the chemistry of 6,6-dibromopenicillanate esters. The recent Merck work describes transmetallation between benzyl 6,6-dibromopenicillanate 1, and Grignard reagents at -78° in tetrahydrofuran followed by condensation with acetaldehyde to yield predominantly the β (R) hydroxyethylpenicillanate derivative 2.[2] We had independently obtained similar results, but in addition would like to report that the course of the reaction can be markedly influenced by the nature of the solvent and the type of metal cation present.

Reaction of benzyl 6,6-dibromopenicillanate 1 with sec or tert butyl lithium in toluene at -78° followed by condensation of the anion with acetaldehyde gave in 89% yield a mixture of isomers, 2-5. Silica gel chromatography allowed separation of the β hydroxyethyl isomer 2 and the other possible β isomer, 3 present in a 26 to 1 ratio. Assignment of stereochemistry to the diastereomers 2 and 3 was based on a chemical shift difference of 4 Hz for the corresponding protons at C-5.[4] Since through space deshielding of protons by neighboring groups is a well documented phenomenon,[5] the S stereochemistry was assigned to 3, the substance exhibiting the downfield shift for H5. The diastereomeric pair 4 and 5 was isolated as an inseparable equicomponent mixture. Interestingly, aldolization in toluene produced an α to β ratio (4 + 5:2 + 3) of 6 to 4 as compared to the corresponding ratio of 1 to 4 produced in tetrahydrofuran. The solvent clearly plays an integral role in the stereotopic formation of the carbon-carbon bond.



Solvation effects were noted in protonation studies as well. The anion generated from 1 with tert-butyl lithium in toluene at -78° produced upon treatment with acetic acid at -78°, a 3:2 mixture of benzyl 6-α-bromopenicillanate 6 and 6-β-bromopenicillanate 7. If, however, the anion is first treated with tetrahydrofuran at -78° (THF:toluene = 3:1) followed by protic quench as above, less than 10% of the β-epimer 7 could be observed. Addition of Toluene to the anion produced in tetrahydrofuran did not conversely increase the amount of 7 relative to 6.



Solvent	6	7
toluene	60%	40%
tetrahydrofuran	100%	0%

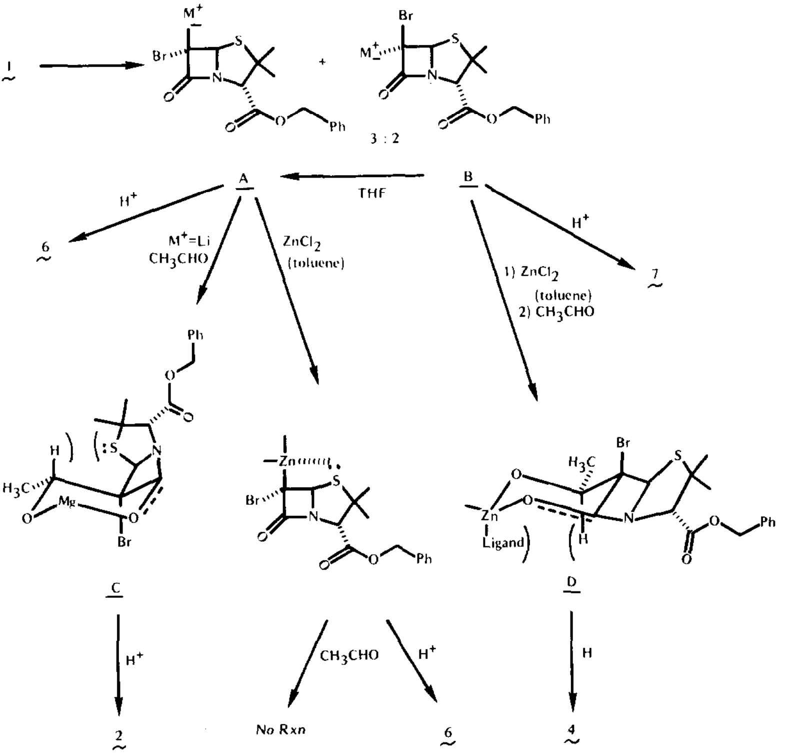
Since zinc ion accommodates ligands to form complexes more readily than either magnesium or lithium,[6] and since stereochemical control of aldol type condensations by zinc enolates is well precedented,[7] the behavior of zinc "enolates"[8] in this reaction was also investigated. Reduction of the dibromo penicillanate 1 in toluene at -78° with sec or tert butyl lithium followed by addition of a concentrated solution of anhydrous zinc chloride in tetrahydrofuran[9] (from 1/2 to 1 equivalent of zinc ion) and acetaldehyde produced benzyl 6-α-bromopenicillanate 6[3] and a single crystalline aldol product mp 124-125°, which proved to have structure 4[2] each in approximately 40% yield. Analysis by nmr and thin layer chromatography showed less than 5% product with the β-hydroxy alkyl side chain (2 or 3). The absolute (S) configuration of the carbon bearing hydroxyl in 4 was determined by reductive dehalogenation of 4 and comparison of the resultant products with those obtained from reduction of the pure 6-α-bromo isomers 2 and 3.[2]

The remarkable stereochemical consequences of these transformations merit consideration. Predominant addition to the hindered β-face of a penicillin modecule (tetrahydrofuran as solvent) was quite surprising in view of literature precedent.[10] Preferential addition to the highly hindered β-face in the more polar solvent indicates that carbanionic localization on the concave side of the molecule is facilitated, possibly through elimination of steric crowding between the remaining bromine atom and the β-methyl group and/or the sulfur lone pair.[11] Formation of carbon-carbon bonds with retention of configuration at the more hindered face is well documented for alicyclic Grignard (tetrahedral carbanion) reactions.[12] The R configuration of the major aldol product 2 presumably results from the nature of the chelate C with the conformationally favored equatorial (R) methyl group directing stereoselection as described by House[7] and others.[13]

Absence of addition to the β-face in the presence of zinc ion suggests that a zinc-carbon bond on the more hindered β-face might be rendered less reactive to aldolization, possibly due to steric factors or through interaction with an electron pair on the adjacent sulfur atom (intermediate A M^+ = Zn) while intermediate B alkylates readily.

Again, the configuration at the side chain carbon bearing hydroxyl may be rationalized by analysis of the transition state for the aldolization.[13] Zinc cations readily form tetrahedral complexes (unlike magnesium and lithium).[5] Tightly bound ligands at the metal atom in the aldol chelate D would likely experience non-bonded interactions, in 1,3 diaxial fashion, with the methyl group of an incoming acetaldehyde molecule in the pro-(R) cyclic transition state. The less sterically congested pro-(S) transition state is therefore favored. The lack of stereoselection at the α-face with the magnesium or lithium enolates may be due to weaker metal ligand bonds for a noncomplexed (solvated) metal cation resulting in an insignificant energy difference for the axial and equatorial methyl substituents.

These experiments exemplify, through judicious choice of solvent and cation, excellent control of stereochemistry in aldol condensations. Our results are reasonably interpreted in terms of a non-planar β-lactam "enolate" whose stereochemistry appears to be mediated by metal ion solvation[11] as well as conformational analysis of aldol transition states[7,13] and complement rapidly evolving methodology for control of stereochemistry in organic syntheses.[13,14]



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