Tetrahedron Letters,Vol.27,No.14,pp 1545-1548,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

STEREOSELECTIVITY IN 6-HALOPENICILLANATE GRIGNARD REACTIONS

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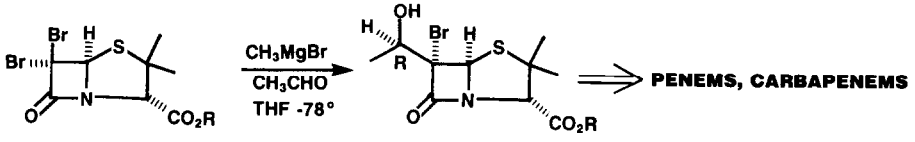
Summary: Structural modifications of 6-halopenicillanate Grignards result in increased "aldol" stereoselectivity. The intermediacy of tetrahedral penicillin carbanions in THF and β-lactam enolates in CH_2Cl_2/toluene is proposed.

An enormous effort has been focused in recent years on the synthesis of carbapenems (thienamycin)[1], penems[2] and other β-lactams bearing a C-6 hydroxyethyl group because of the remarkable biological activity of the these antibiotics. Penicillin-based syntheses of these compounds require a hydroxyethylation process capable of establishing the requisite C-8 (R) stereochemistry. The Grignard acetaldehyde condensation shown below, which was first reported by DiNinno, *et. al.*[3], serves as the cornerstone of these approaches.



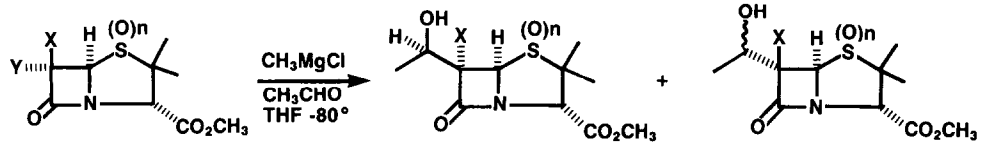
The role that solvent and counterion play in this reaction has been evaluated by Kellogg and Aimetti[4]. In this communication we probe the effect of structural changes on the penicillin framework as a means of influencing the stereochemical outcome of this reaction. Recent publications of Shim, *et. al.*[5], describing a similar approach prompted us to report our results.

Product distribution in the initial penicillin Grignard acetaldehyde addition[3] (Example I) suggested to us that C-8 stereocontrol could be achieved only if facial selectivity (β vs α) is obtained.[6] Furthermore, predominant addition from the more hindered concave (β) face of the penicillin skeleton implicated the intermediacy of a tetrahedral penicillin carbanion[4,7]. We hoped to increase the stereochemical control in this condensation, therefore, by stabilizing such a carbanion on the β-face of the molecule (A) by increasing the size of the remaining C-6 halogen substituent and/or by the generation of penicillin sulfones/β-sulfoxides. (Scheme I)

To this end, methyl dihalopenicillanates 1[8] were generated and treated with methylmagnesium chloride in THF at -80° (0.5 hr) followed by acetaldehyde to give, after an acetic acid quench, mixtures of hydroxyethylated products (Table I). Crude reaction mixtures were assayed by ^1H NMR (300 MHZ) and were resolved by chromatography. Mixed dihalopenicillanates (Examples 2 & 3) led to preferential (not exclusive) formation of the corresponding bromine and chlorine containing Grignard reagents[9]. Since standard samples were not available to confirm the

structures of the iodo and chloro acetaldehyde adducts, the α and β products were subjected to tributyltin hydride reduction to confirm the C-8 stereochemistry since only β-hydroxyethyl penicillanates are formed[10].

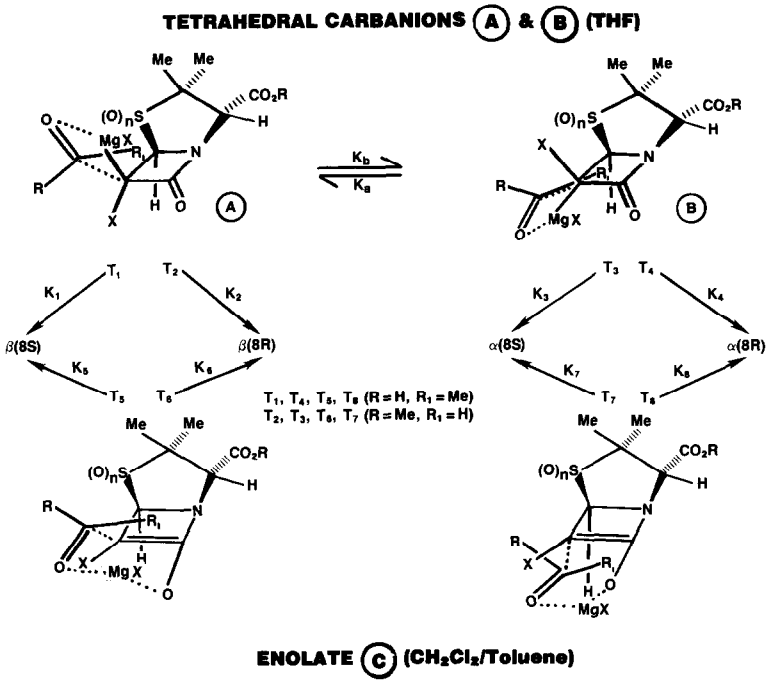
In our hands, bromine replacement did not improve the stereocontrol of the acetaldehyde condensation. Our results differ from those of Shim, *et.al*[5], who report a stereospecific condensation for the diiodopenicillanate derived Grignard reagent (Example 4) . Our attention was next focused on the effect of the thiazolidine sulfur oxidation state on the acetaldehyde condensation. Dihalopenicillanate sulfoxides[11] and sulfones[12] could be obtained by MCPBA treatment of the parent sulfides. Acetaldehyde condensations involving the sulfone or β-sulfoxide containing Grignards (Examples 7-10) resulted in a significant improvement in stereocontrol as increased addition occurs from the more congested β-face. As expected this facial selectivity is accompanied by C-8 stereoselectivity. Replacement of THF with CH_2Cl_2 or toluene, however, caused significant erosion in both facial and stereoselectivity with both sulfide/sulfone bearing Grignards (Examples 11-13).



1 β(8R) α(8R + 8S)

Table I

Example	Dihalopenicillanates1		Solvent	Product	Product Ratio (%) β 8R	β 8S	α 8R	α 8S
				Effect of Halogen Atom Size				
1	X,Y = Br	n = 0[8]	THF	X = Br[3,5]	77	1	5	17
2	X,Y = I, Br	n = 0[8]	THF	X = Br	68	1	5	17
				X = I	7	—		2
3	X,Y = I, Cl	n = 0[8]	THF	X = Cl[5]	65	—	5	25
				X = I	3	—	1	1
4	X,Y = I, I	n = 0[8]	THF	X = I[5]	61	—	7	32
				Sulfur Substitution				
5	X,Y = Br	n = 0[8]	THF	X = Br[3,5]	77	1	5	17
6	X,Y = Br	n = I(α)[11]	THF	X = Br[12]	76	8	3	13
7	X,Y = Br	n = I(β)[11]	THF	X = Br	>98	—	—	—
8	X,Y = Br	n = 2[8]	THF	X = Br[12]	89	—	4	7
9	X,Y = I, Br	n = 2[8]	THF	X = Br	83	—	3	7
				X = I	7	—	—	—
10	X,Y = I, Cl	n = 2[8]	THF	X = Cl	88	—	4	8
				Solvent Effects				
11	X,Y = Br	n = 0[8]	Toluene	X = Br[4]	45	1	33	21
12	X,Y = Br	n = 0[8]	CH_2Cl_2	X = Br	45	—	35	20
13	X,Y = Br	n = 2[8]	CH_2Cl_2	X = Br	39	—	38	23



Scheme 1

We believe the THF Grignard results are consistant with the intermediacy of the THF stabilized tetrahedral carbanions (A&B). Carbanionic localization on the more hindered β-face (A) of the sulfones/β-sulfoxide would be stabilized by sulfoxide/sulfone chelation and furthermore would eliminate strain caused by interaction of the remaining halogen atom and the thiazolidine β-methyl group and the proximal sulfoxide/sulfone moieties. Small electrophiles capable of magnesium coordination would be directed to the β-face[13]. Steric congestion on the β-face imposed by the penicillin framework would dictate excellent C-8 stereocontrol (diastereoisomeric transition state T_2 would be preferred over T_1). (Scheme I). In all cases, α-face stereocontrol is poor and presumeably reflects a diminished steric bias for one of the two tetrahedral transition states (T_3 vs T_4).

On the other hand, the toluene (CH_2Cl_2) results are consistent with the intermediacy of a β-lactam enolate (C) as significant addition from the more accessible α-face occurs.[14] The large amount of 8R isomer resulting from α addition supports this hypothesis since transition state T_8 would avoid nonbonded halogen/methyl interactions present in T_7. Stereospecific aldolization from the β-face would again be dictated by steric congestion on the concave face (preference of T_6 vs T_5).

In summary, the stereospecificity of the hydroxyethylation process of the ambident halopenicillanate anions are solvent/structure dependent. β-Sulfoxide and sulfone dihalopenicillanates provide improved Grignard stereoselectivity. Application of this technology in the synthesis of key carbapenem/penem intermediates will be reported.

Acknowledgement. We express our gratitude to Drs. Yuhpyng Chen and Michael Kellogg and other colleagues at Pfizer for stimulating discussions.

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6. β-Addition provides predominantly the desired C-8 stereochemistry. α-Addition, however, results in a mixture of isomers, the majority of which is undesired (C-8(s)).

7. The intermediacy of a penicillin pyrimidal carbanion is implicated in work of Firestone, *et al*, in their studies on the epimerization of 6-aminopenicillanic acid. See R. A. Firestone, N.S. Maciejewicz, R. W. Ratcliffe and B. G. Christensen. *J. Org Chem* **39** 437 (1974). H. Hirai, K. Sawada, M. Aratani and M. Hashimoto, *Tetrahedron Letters* **1739** (1985). For recent examples of non β-lactam heteroatom-substituted tetrahedral carbanions see: J. S. Sawyer, T. L. MacDonald and G. J. McGarvey *J. Amer. Chem. Soc.* **106** 3376 (1984) and references therein.

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9. While this result demonstrates that the more hindered β-iodo atom is preferentially removed, the selectivity in the dibromopenicillinate Grignard exchange is unknown.

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12. K. Hirai, Y. Iwano, Japanese Patent Application 55-176303, Sankyo Co. (1982).

13. We assume with this proposed model that, as in the aldol condensation, metal chelation delivers the incoming electrophile. While we know little about the state of aggregation of these anions, we do know that facial selectivity erodes with the addition of larger aldehydes/ketones which suggests that carbanion equililbration (A⇆B) occurs on the time scale of the Grignard additions. With the sulphone/β-sulfoxide acetaldehyde condensations in THF, our proposed model implies $K_a \times K_2 >> K_b \times K_3$ or K_4 (Scheme I).

14. Kinetic protonation studies (AcOH) of the anions in CH_2Cl_2 or toluene result in similar erosion of facial selectivity.

(Received in USA 19 December 1985)