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SYNTHETIC AND MECHANISTIC STUDIES INVOLVING THE CONDENSATION OF PENICILLIN GRIGNARDS AND BORON TRIFLUORIDE ACTIVATED OXIME ETHERS

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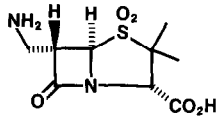
Summary: High stereocontrol is observed in the BF_3 mediated condensation of anions derived from mono and dibromopenicillanic ester sulfones and oxime ethers.

Recently a series of β-lactamase inhibitors (I) having a C-6 (penicillin) aminomethyl substituent has been reported by Barth.[1] While somewhat lengthy methods have been developed to generate aminomethyl penicillins,[2] we reasoned that the addition of penicillin Grignard 2[3] to a formaldehyde imine equivalent should provide a more straightforward entry into this molecular framework (Scheme I).



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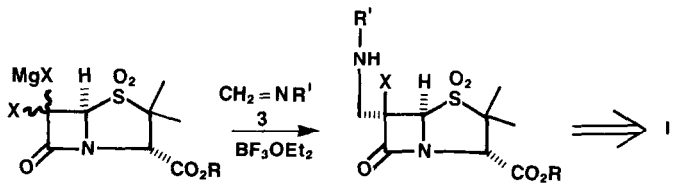
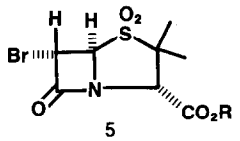
Due to the instability of formaldehyde imine **3** (R' = H),[4] we first sought an aminomethylating agent[5] which would be stable to storage yet reactive enough at temperatures (-80°) required to ensure dibromopenicillanate sulfone Grignard (2) stability. Ethyl formaldoxime **3** (R' = OEt)[6,7] seemed to fill these requirements and was generated in high yield by the reaction of ethoxyamine and aqueous formaldehyde. Treatment of sulfone Grignard **2** (X = Br, R = $CH_2Ø$) with an equivalent of ethyl formaldoxime **3** in THF at -80° gave no indication of product



2 4

Scheme 1

formation. Warmer temperatures led to Grignard degradation. The addition of an equivalent of $BF_3{\cdot}OEt_2$[8] however to the Grignard/formaldoxime solution (-80°, THF) resulted after an acetic acid quench in the isolation of ethoxyamine **4** (X = Br, R = $CH_2Ø$),[9,10] mp 136-138, in 70% yield. Single crystal X-ray analysis established the C-6 α-ethoxyaminomethyl configuration.[11] 6-α-Bromopenicillanate sulfone **5**[12] was similarly converted to its corresponding Grignard **2** (X = H, R = $CH_2Ø$) and treated with ethyl formaldoxime **3** utilizing the abovementioned conditions to generate α-ethoxyaminomethyl adduct **4** (X = H, R = $CH_2Ø$)[9,13] in 40% yield.



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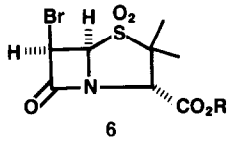

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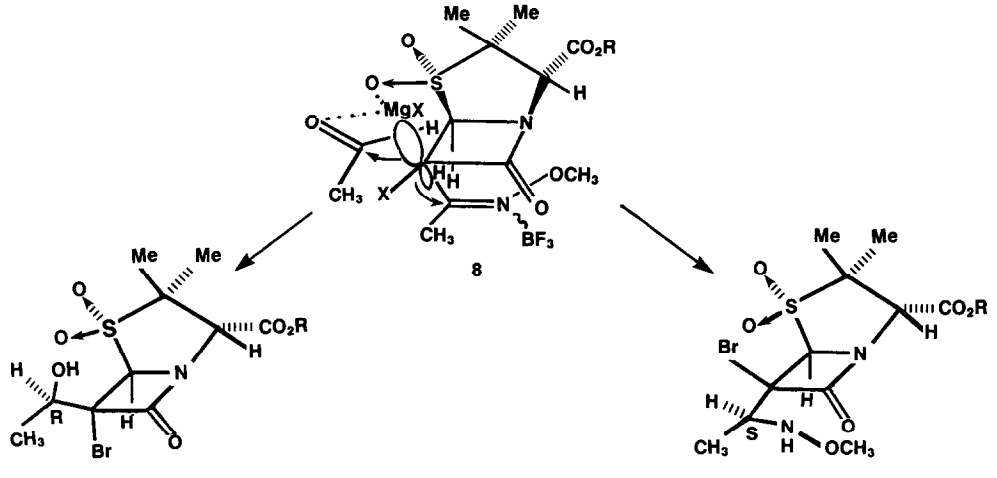
The predominant addition of formaldoxime **3** to the convex α-face of the penicillin nucleus is particularly noteworthy since acetaldehyde addition occurs predominantly from the β-face to give **7**.[3] In an attempt to learn more about the factors which govern the oxime facial selectivity, we decided to examine the condensation of sulfone Grignard **2** (X = Br, R = Me) and acetaldehyde methoxime **8** since the expected product would not only reveal C-6 facial selectivity but also added stereochemistry in the form of an additional stereogenic center. In the event, acetaldehyde methoxime **8** addition (BF_3, -80°, THF, 2 hr) generated stereoselectively methoxime **9**[9,11] in 35-40% chromatographed yield. In addition to product, the reaction mixture contained α and β-bromopenicillanates **5**[9] and **6**[9], the products of Grignard protonation.[14]



Scheme 2

We believe the presence of the sulfone moiety is a key determinant in the facial selectivity of the Grignard additions.[15] Whereas acetaldehyde can be preferentially delivered to the more hindered β-face of the penicillin framework by a chelation stabilized Grignard, a boron trifluoride activated oxime ether does not benefit from metal coordination (Scheme 2). Therefore, anion accessibility is the key factor in determining the course of the oxime

additions. As in other SE_2 condensations (assuming our tetrahedral carbanion model), addition need not involve prior anion inversion but can result from attack on the rear lobe of the chelation stabilized carbanion (Scheme 2). C-8 stereocontrol in the methoxime addition is consistent with this hypothesis as nonbonded oxime/β-lactam interactions on the convex (α)-face of the molecule would favor the oxime transition state[16] depicted in Scheme 2.

While the rationale for facial and stereoselectivity is, at this stage, speculative, the ability of electrophiles to effect diastereofacial selectivity is precedented.[17] Elegant mechanistic studies involving the alkylation of lithiated cyclohexane N,N-dialkylhydrazones by Collum, *et al.*,[18] for example, suggest alkylations (similar to the BF_3-oximes) occur opposite to a π-complexed lithium, as stereoelectronic and face coordination preferences work in concert to afford high axial selectivity. With the addition of aldehydes, these preferences are in opposition, and facial selectivity erodes. Recently, Meyers, *et al.*[19] demonstrated opposite facial selectivity in the alkylation and protonation of dipole stabilized tetrahydroisoquinoline carbanions.

The ethoxyaminomethyl sulfones **4** generated in the abovementioned Grignard additions serve as convenient aminomethyl penicillin intermediates. Hydrogenolysis of **4** (R = $CH_2Ø$, X = H) *via* Raney nickel (50 psi H_2, CH_3OH/H_2O) provided **19** in 50% yield. Details of these and other studies[20] will be reported elsewhere.

Acknowledgements - We express our gratitude to Dr. Jon Bordner for X-ray crystallographic support and to Professors Stuart Schreiber and David Collum and to Dr. Edward Kleinman and other colleagues at Pfizer for stimulating discussions.

References and Notes

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3. B. B. Brown and R. A. Volkmann, *Tetrahedron Letters* 000 (1986). K. Hirai, Y. Iwano, Japanese Patent Application 55-176303, Sankyo Co. (1982).

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5. For recent examples see: H. J. Bestmann and G. Wolfel, *Ang. Chem.* **23**, 53 (1984). K. Okano, T. Morimoto and M. Sekiya, *J. Chem. Soc., Chem Commun.* **883** (1984). L. E. Overman and R. M. Burk. *Tetrahedron Letters*, **1635** (1984) and references therein.

6. This compound (Bp. 36°) was made by the method of K. A. Jensen, L. Buus and A. Holm, *Acta Chemica. Scand.* B **31**, 28 (1977). Methyl formaldoxime was also condensed with penicillin Grignards, but was less useful due to its extreme volatility (Bp 12°). Caution: Although its toxicity is unknown, the established toxicity of hydroxylamine ethers (Dangerous Properties of Industrial Material, 5th ed. by N. I. Sax, page 805) would suggest that these compounds be handled with due care.

7. Recently N-benzyloxyimines have been utilized for the synthesis of monocyclic β-lactams, see K. Ikeda, K. Achiwa and M. Sekiya. *Tetrahedron Lett.* **24**, 4707 (1983). K. Ikeda, Y. Yoshinaga, K. Achiwa and M. Sekiya, *Chem. Lett.* **369** (1984).

8. A similar activation of imines (3-thiazolines) with BF_3 led to a recent synthesis of d-biotin. See: R. A. Volkmann, J. T. Davis and C. N. Meltz. *J. Amer. Chem. Soc.* **105**, 5946 (1983). For other examples see: C. N. Meltz and R. A. Volkmann, *Tetrahedron Letters* **4503**, **4507** (1983). M. Wada, Y. Sakurai and K. Akiba, *ibid.* **1079**, **1083** (1984).

9. Satisfactory spectral and analytical data was obtained for this compound.

10. A small amount (<5% yield) of an additional imine adduct whose NMR spectra was consistent with the 6-β-ethoxyaminomethyl isomer of **4** was isolated.

11. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication.

12. A sample of **5** was made by $NaHSO_3$ reduction of dibromopenicillanic acid sulfone followed by esterification. A sample of **6** was made by $(nBu)_3SnH$ reduction of dibromopenicillanate sulfone following the procedure of J. A. Aimetti, E. S. Hamanaka, D. A. Johnson and M. S. Kellogg, *Tetrahedron Letters* **4631** (1979).

13. This compound was also synthesized by zinc reduction[21] of **4** (X = Br) and showed the typical $J_{5,6}$ (^1H) coupling of <2 Hz. The β-ethoxyaminomethyl isomer could also be made by $(nBu)_3SnH$ reduction[12] and showed $J_{5,6}(^1H)$ coupling of 4Hz.

14. The generation of monobromopenicillinate sulfones **5** and **6** is not surprising. Acetaldehyde methoxime **8** exists as a mixture of geometric isomers. In examining the addition of other nucleophiles to BF_3 activated aliphatic oximes, we noticed that, in general, nucleophiles add to oxime ethers possessing an anti-configuration and preferentially deprotonate those having a syn configuration. The configurational preferences for oxime anion formation has been examined. See: T. A. Spenser, C. W. Leong, *Tetrahedron Letters* **3889** (1975). R. R. Fraser, K. L. Dhawan, *J. Chem. Soc. Chem. Commun.* **674** (1976). H. E. Ensley and R. Lohr, *Tetrahedron Letters* **1415** (1978).

15. In the course of this work, we explored the BF_3 oxime additions of dibromopenicillanate (sulfur) derived Grignards. Product mixtures were obtained in which the major product (~3:1) has β-ethoxyaminomethyl substitution.

16. While we invoke a tetrahedral transition state to rationalize product stereochemistry, C-8 stereoselectivity in both the aldehyde/oxime additions are yet two more of a growing list of reactions which support the topological rule for donor-acceptor double bond reactions described by Seebach (D. Seebach and J. Golinski, *Helv. Chem. Acta* **64**, 1413 (1981).

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19. M. F. Loewe, M. Boes and A. I. Meyers, *Tetrahedron Letters* 3295 (1985).

20. In the presence of BF_3, formaldoximes 3 are useful dienophiles and provide entry into a variety of heterocycles. We are in the process of exploring this chemistry.

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