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THE PREPARATION OF THE FIRST α-VINYLIDENEPENAMS

John D. Buynak*, H. B. Borate, Chad Husting, Trace Hurd, Jyoti Vallabh, Jacob Matthew, Jarvis Lambert and Upali Siriwardane

Department of Chemistry, Southern Methodist University, Dallas, TX 75275

Abstract: Benzyl esters of the first 6-vinylidenepenams have been prepared by reaction of 6-position propargylic triflates with higher order organocuprates. This methodology permits a great deal of versatility in the introduction of substituents at the terminal allenyl position.

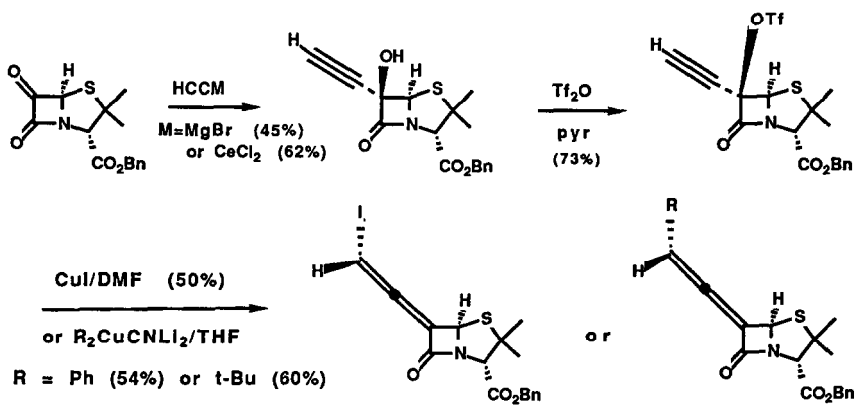
Our interest in allene chemistry, β-lactams, and strained organic molecules recently led us to prepare the first β-lactam with a fused allene alpha to the carbonyl.[1] However, these primarily monocyclic β-lactams did not possess the relatively strained, highly functional, bicyclic skeletons common to many of the biologically active molecules (ex. penams, penems, cephams, carbapenems, etc.). The bicyclic β-lactam antibiotics continue to interest the biochemical and medicinal community. Recently, for example, Merck workers demonstrated that certain cephams (as their sulfone *esters*) have biological activity as elastase inhibitors.[2] Due to our previous interest in the chemistry of allenes and since the allene unit has played a key role in the preparation of other mechanism-based, non-β-lactam enzyme inhibitors,[3] we decided to attempt to fuse an allene to the 6-position of a penam. We would now like to report that we have succeeded in generating the first 6-vinylidenepenam esters. We believe the structural diversity permitted by our synthesis will facilitate the preparation of numerous examples for biological evaluation.

The route to these compounds is shown in Scheme I. Treatment of benzyl 6-oxopenicillinate, prepared in the usual manner[4,5] with magnesium acetylide or the cerium acetylide[6] results in the formation of the corresponding propargylic alcohol. Conversion to the triflate, followed by careful treatment with a cuprate (at -78° C for the higher order curpates, and at room temperature with cuprous iodide) produces the 6-vinylidenepenam.[7] Although other investigators have shown that direct nucleophilic substitution of leaving

groups at the 6-position of the penam skeleton by carbon nucleophiles is not feasible,[8] this is the first time such a displacement has been attempted in a vinylogous fashion. It is of interest to note that this displacement was stereospecific when performed with either cuprous iodide in DMF or with the higher order cyanocuprates in THF, but resulted in an approximately 1:1 mixture of diasteriomers when performed with CuI/LiI in THF. This is in contrast to the results of Vermeer,[9] who stereoselectively obtained chiral iodoallenes from the corresponding chiral propargylic mesylates using the latter system. It was extremely important to limit the exposure of these allenes to organocuprates to avoid unwanted (and often inseparable) addition products. Thus, reaction times were limitted to 3 min. at - 78°C in the formation of the phenyl and *t*-butyl allene.

The presence of an allene is unambiguously comfirmed by the appearance of a new absorption in the ^{13}C NMR spectrum of each allene at 195 to 198 ppm (the central carbon of the allene), as well as an absorption at 1960 cm^{-1} in the infrared (allene stretch).[10] The ^{1}H NMR of each product showed a new vinylic absorption in the range 5.87 (for the *t*-butyl allene) to 6.83 (for the phenyl allene) which has a very small coupling constant (1.5 Hz) with the proton at C-5.[11] All other absorptions, including the carbonyl absorptions at 1760 to 1780 cm^{-1}, remain relatively constant, confirming the fact that no unexpected rearrangement has occurred. Although we have, as yet, not obtained crystals suitable for x-ray diffraction, we propose that the overall substitution occurs in an *anti* fashion (in agreement with literature precedent[12]). The α-vinylidenepenams are reasonably stable, surviving column chromatography on silica gel and normal handling procedures at room temperature. We are currently in the process of exploring the chemistry and biochemistry of these materials and will report our results shortly.

Scheme I



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[2]Doherty, J. B. *et. al. Nature* **1986**, *322*, 192.

[3]For leading references, see: *Enzyme-Activated Irreversible Inhibitors*; Seiler, N.; Jung, M. E.; Koch-Weser, J., Eds.; Elsevier/North Holland Biomedical Press: Amsterdam, 1978. b) Castelhano, A. L.; Pliura, D. H.; Taylor, G. J.; Hsieh, K. C.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 2734. c) Spencer, R. W.; Tam, T. F. Thomas, E.; Robinson, V. J.; Krantz, A. *J. Am. Chem. Soc.* **1986**, *108*, 5589. d) Schwab, J. M.; Ho, C.; Li, W.; Townsend, C. A.; Salituro, G. M. *J. Am. Chem. Soc.* **1986**, *108*, 5309.

[4]Chen, Y. L.; Chang, C. W.; Hedberg, K.; Guarino, K.; Wesch, W. M.; Kiessling, L.; Retsema, J. A.; Haskell, S. L.; Anderson, M.; Manousos, M.; Barrett, J. F. *J. Antibiotics*, **1987**, *40*, 803.

[5]It should be noted that derivatives of 6-oxopenicillanic acid are extremely sensitive toward contact with aqueous solutions at pH7. Care must be taken to buffer all washings with NH_4Cl. In our hands, these materials were unstable to column chromatography. We thank Dr. Y. L Chen for advice on the handling of these compounds.

[6]Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Pharm. Bull.* **1986**, *34*, 1531.

[7]All allenes have been characterized by elemental analysis and/or high resolution mass spectroscopy as well as ^1H NMR, ^{13}C nmr, and IR.

[8]a)Kemp, J. E. G.; Closier, M. D.; Narayanaswami, S.; Stefaniak, M. H. *Tetrahedron Lett.* **1980**, *21*, 2991. b) Hanessian, S.; Alpegiani, M. *Tetrahedron Lett.* **1986**, *27*, 4857.

[9]Elsevier, C. J.; Vermeer, P.; Gedanken, A.; and Runge, W. *J. Org. Chem.* **1985**, *50*, 364.

[10]**Iodoallene:**
Anal. Calcd for $C_{17}H_{16}NO_3SI$: C, 46.27; H, 3.65; N, 3.17; I, 28.76. Found: C 45.86; H, 3.71; N, 3.12; I, 27.52.
HRMS Calcd for $C_{17}H_{16}NO_3Si$: 440.9897; Found 440.9907.
IR ($CHCl_3$) 1958, 1778, and 1740 cm^{-1}
^{1}HNMR ($CDCl_3$) δ 7.39 (brs, 5H), 6.56 (d, J = 1.3 Hz, 1H), 5.94 (d, J = 1.3 Hz, 1 H), 5.21 (s, 2 H), 4.56 (s, 1H), 1.61 (s, 3 H), 1.42 (s, 3 H).
^{13}CNMR ($CDCl_3$) δ 195.0, 167.4, 165.5, 134.6, 128.7, 110.8, 70.3, 67.4, 67.1, 65.1, 43.6, 33.3, 25.8.

***t*-butylallene:**
Anal. Calcd for $C_{21}H_{25}NO_3S$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.39; H, 6.63; N, 3.71.
HRMS Calcd. for $C_{21}H_{25}NO_3S$, 371.1557; Found 371.1569.
IR ($CHCl_3$) 1965, 1760, and 1745 cm^{-1}.
^{1}HNMR ($CDCl_3$) δ 7.40 (br s, 5 H), 5.87 (d, J = 1.5 Hz, 1 H), 5.84 (d, J = 1.5 Hz, 1 H), 5.22 (br s, 2 H), 4.54 (s, 1 H), 1.61 (s, 3 H), 1.42 (s, 3 H), 1.13 (s, 9 H).

^{13}CNMR ($CDCl_3$) 194.2, 169.0, 168.0, 134.9, 128.6, 112.0, 110.0, 70.1, 68.9, 67.3, 64.8, 33.5, 32.9, 29.8, 26.0.

phenylallene:
HRMS Calcd. for $C_{23}H_{21}NO_3S$ 391.1243. Found: 391.1253.
IR ($CHCl_3$) 1950, 1760, 1740 cm^{-1}.
^{1}HNMR ($CDCl_3$) δ 7.41 (br s, 5 H), 7.35 (br s, 5 H), 6.83 (d, J = 1.5 Hz, 1 H), 5.99 (d, J = 1.5 Hz, 1 H), 5.24 (s, 2 H), 4.61 (s, 1H), 1.66 (s, 3 H), 1.45 (s, 3 H).
^{13}CNMR ($CDCl_3$) δ 198.2, 167.8, 165.5, 130.0, 111.5, 102.9, 70.2, 68.9, 67.4, 65.1, 33.1, 25.9.

[11]This is a reasonable value for the five bond coupling in allenic systems: a) Snyder, E. I.; Roberts, J. D. *J. Am. Chem. Soc.* **1962**, *84*, 1582. b) Hanna, M. W.; Harrington, J. K. *J. Phys. Chem.* **1963**, *67*, 940. c) Samtelli, M. *J. Chem. Soc. Chem. Commun.* **1971**, 938.

[12]a) Elsevier, C. J.; Meijer, J.; Westmijze, H.; Vermeer, P.; Dijck, L. A. *J. Chem. Soc. Chem. Commun.* **1982**, 84. b) Haces, A.; van Kruchten, E. M. G. A.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 2707. c) See ref. 1 of Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3059.

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