Tetrahedron Letters,Vol.29,No.20,pp 2409-2412,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

2-AZA-1,3-DIENES AS NOVEL PRECURSORS FOR THE SYNTHESIS OF N-UNSUBSTITUTED β-LACTAMS. A THREE STEP SYNTHESIS OF 4-ACETOXY-3-PHENOXY-2-AZETIDINONE

Gunda I. Georg*, Joydeep Kant, Ping He,
Ana Maria Ly and Lynn Lampe[1]

Department of Medicinal Chemistry
University of Kansas
Lawrence, KS 66045-2500 U.S.A.

Abstract: 2-Aza-1,3-dienes, prepared in excellent yields from aldehydes and readily available allylamine, were utilized to synthesize N-(1-propenyl)-β-lactams. Oxidative cleavage of the N-protecting group produced N-unsubstituted β-lactams. 4-Acetoxy-3-phenoxy-2-azetidinone was synthesized in three steps and 34% overall yield.

In connection with our studies on the stereo- and enantioselective synthesis of β-lactams,[2] we were interested in devising novel N-protecting groups for β-lactam synthesis, which can be deprotected easily and under mild reaction conditions. N-Unsubstituted β-lactams are useful and necessary intermediates for the preparation of a variety of β-lactam antibiotics and related analogues.[3] Although the Bose procedure[4] has been widely explored for the synthesis of β-lactams, only a few number of amines have been utilized.[4,5]

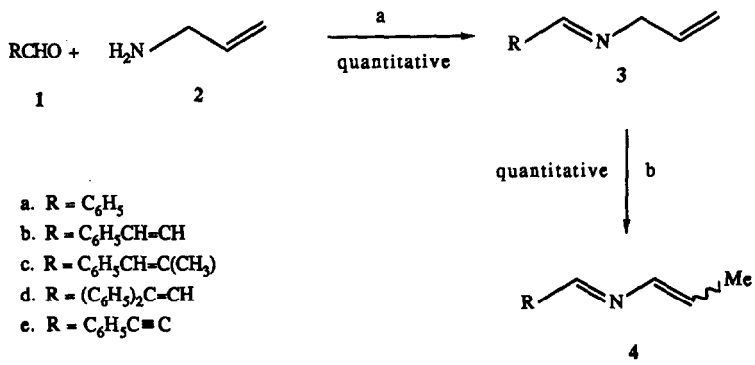
We wish now to report that commercially available allylamine 2 can be utilized[6] to synthesize 2-aza-1,3-dienes 4. We have explored the utility of these 2-aza-1,3-dienes 4 as novel precursors for β-lactam preparation via the acid chloride-imine methodology. The resulting N-(1-propenyl)-β-lactams (Figure) were deprotected oxidatively in one or two steps. Although 2-aza-1,3-dienes have found some utility as useful synthons for nitrogen containing heterocycles,[7] little attention has been paid to appreciate azadienes in β-lactam synthesis.[8]

The 2-aza-1,3-dienes 4a-4e utilized in our studies were prepared in quantitative yields in a one flask, two step procedure (Scheme I).[9] Reaction of allylamine 2 with several aldehydes 1 produced the imines 3, which were subsequently isomerized with 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) in methylene chloride to yield the desired 2-aza-1,3-dienes. The dienes 4 were obtained as a mixture of E and Z isomers, which could not be separated by chromatography or distillation. Imines of type 3 obtained from enolizable aldehydes however, could not be isomerized to the corresponding 2-aza-1,3-dienes 4.

The newly synthesized 2-aza-1,3-dienes 4 were subsequently investigated in the acid chloride imine reaction to yield the expected β-lactams 5-10 in good to moderate yields (Figure). Optimum yields in the β-lactam formation were observed when the 2-aza-1,3-dienes were freshly prepared.

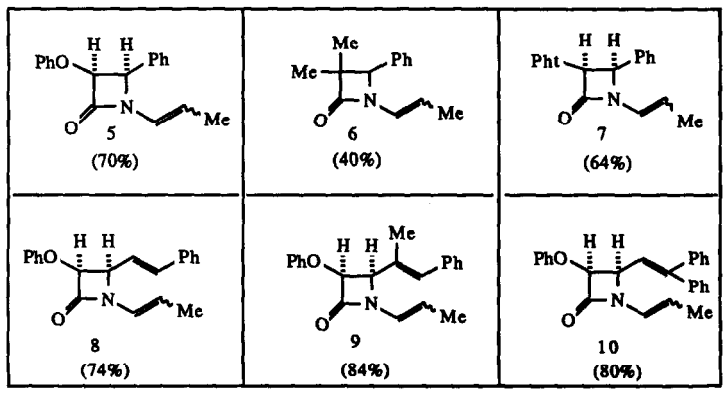
It is noteworthy that β-lactam formation proceeded exclusively with cis stereochemistry in all cases observed. Recent reports have indicated that cis-stereoselectivity is favored in the acid halide-imine method when the bulk of the N-substituent is increased[10] and also when

Scheme I



(a) Neat, 1h, 25° C; (b) DBU, CH_2Cl_2, overnight, 25° C.

Figure. β-Lactams Prepared (Yields)



cinnamylidene Schiff bases are employed in the reaction.[11]

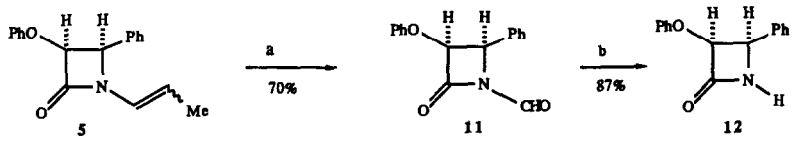
N-Vinyl derivatives of β-lactams have previously been recognized as valuable precursors for N-unsubstituted β-lactams.[12] However, the N-vinyl substituents were usually synthesized by multistep functional group transformations after β-lactam formation.

The advantage of our methodology lies then in the convergent approach to introduce the N-(1-propenyl) group simultaneously with β-lactam formation, thus requiring only one or two steps for the deprotection of the β-lactam.

Deprotection of the N-(1-propenyl) β-lactams could be achieved in a two step sequence (Scheme II). When β-lactam 5 was subjected to ozonolysis or treatment with osmium tetroxide and sodium periodate, N-formyl β-lactam 11 was obtained in 70% yield. Subsequent oxidation with potassium permanganate in tetrahydrofuran/water completed the deprotection to give the N-unsubstituted β-lactam 12 in 87% yield.

The utility of our novel approach could also be demonstrated for the synthesis of N-unsubsti-

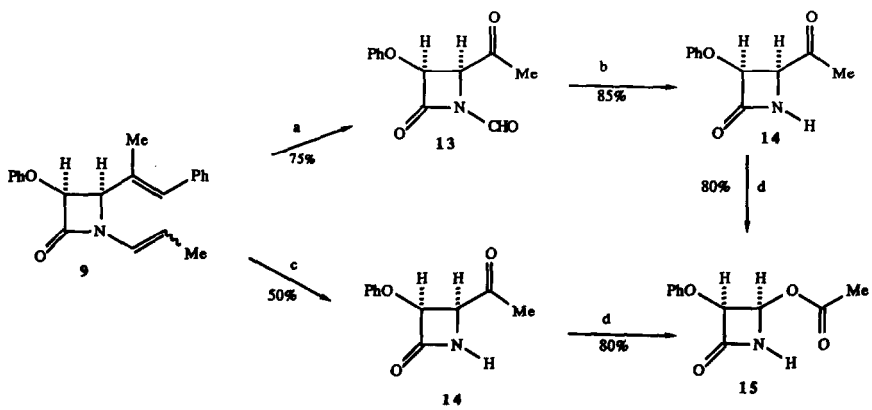
Scheme II



(a) O_3, CH_2Cl_2, -78°, Me_2S or $NaIO_4$, OsO_4, THF-H_2O, 14h, 25°C ; (b) $KMnO_4$, THF-H_2O, 4h, 25° C.

tuted 4-acetoxy-2-azetidinones, which are important building blocks for the synthesis of penem and carbapenem antibiotics.[13] Simultaneous cleavage of the two double bonds in β-lactam 9 (Scheme III) via ozonolysis produced the N-formyl-4-acetyl derivative 13 in 75% yield. Treatment of β-lactam 13 with potassium permanganate yielded then the N-unprotected β-lactam 14 in 85% yield. Deprotection of β-lactam 9 in a one step sequence with potassium permanganate in acetone produced the N-unsubstituted β-lactam 14 in 50% yield. The desired 4-acetoxy-2-azetidinone 15 could be obtained through Baeyer-Villiger oxidation of 14 in 80% yield. Thus, 4-acetoxy-2-azetidinone 15 could be synthesized in three steps in 34% overall yield and in four steps in 43% overall yield from readily available 2-aza-1,3-diene 4c. With this paper we have demonstrated the utility of 2-aza-1,3-dienes in the formation of N-unsubstituted β-lactams.

Scheme III



(a) O_3, CH_2Cl_2, -78° C, Me_2S; (b) $KMnO_4$, THF:H_2O, 4h, 25° C; (c) $KMnO_4$, acetone, 16h, 25° C; (d) m-CPBA, $CH_3COOC_2H_5$, reflux, 5h.

Dedication: This paper is dedicated to Prof. H. Böhme on the occasion of his 80th birthday.

Acknowledgements: Financial assistance from the National Institutes of Health (Grant 21612), The American Heart Association of Kansas (KS-87-G-17) and the Biomedical Research Grant (RR 5606) at the University of Kansas is acknowledged.

References and Notes:

(1) Participant of the Summer Undergraduate Research Program at the Department of Medicinal Chemistry at the University of Kansas in 1986 and 1987. Recipient of the Undergraduate Summer Research Sterling Winthrop Fellowship and an Undergraduate Research Honors Fellowship from the University of Kansas.

(2) Georg, G. I., Kant, J.; Gill, H. S. J. Am. Chem. Soc. 1987, 109, 1129.

(3) For review: Morin, R. B.; Gorman, M. Chemistry and Biology of β-Lactam Antibiotics; Academic: New York, 1982; Vol. 1-3.

(4) Bose, A. K.; Anjaneyula, B.; Bhattacharya, S. K.; Manhas, M. S. Tetrahedron 1967, 23, 4769.

(5) (a) Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. J. Am. Chem. Soc. 1977, 99, 2353. (b) Fukuyama, T.; Frank, R. K.; Jewell, C. F. J. Am. Chem. Soc. 1980, 102, 2122. (c) Heck, J. V.; Christensen, B. G. Tetrahedron Lett. 1981, 22, 5027. (d) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. J. Orq. Chem. 1982, 47, 2765. (e) Fukuyama, T.; Laird, A.; Schmidt, C. A. Tetrahedron Lett. 1984, 25, 4709. (f) Bose, A. K.; Hegde, V. R.; Wagle, D. R.; Bari, S. S.; Manhas, M. S. J. Chem. Soc., Chem. Commun. 1986, 161. (g) Cossio, F. P.; Lecea, B.; Palomo, C. J. Chem. Soc., Chem. Commun. 1987, 1743.

(6) Allylamine has been utilized before in β-lactam synthesis via the acyl halide-imine method (ref. 5e). The deprotection to form the N-unsubstituted β-lactam, however, required four steps.

(7) For a review see: Boger, D. L. Tetrahedron 1983, 39, 2869. Also see: Armesto, D.; Bosch, P.; Horspool, W. M.; Ortiz, M. J. Tetrahedron Lett. 1987, 28, 4065. Böhme, H.; Ingendoh, A. Chem. Ber. 1979, 112, 1297. Armesto, D.; Gallego, M. G.; Horspool, W. M.; Ortiz, M. G.; Perez-Ossorio, R. Synthesis 1987, 657 and references cited there.

(8) One example for the utilization of 1,4-diphenyl-2-aza-1,3-diene in β-lactam synthesis via the lithium ester enolate imine condensation has been reported. Komatsu, M.; Yamamoto, S.; Ohshiro, Y.; Agawa, T. Heterocycles 1985, 23, 677.

(9) 2-Aza-1,3-diene 4a has been previously synthesized in good yields through isomerization of imine 3a with tert-butoxide in dimethyl sulfoxide, a methodology which failed for the synthesis of 2-aza-1,3-dienes 4b-4e. Worley, S. D.; Taylor, K. G.; Venugopalan, B.; Clark, M. S. Tetrahedron 1978, 34, 833.

(10) (a) Moore, H. W.; Hughes, G.; Srinivasachar, K.; Fernandez, M.; Nguyen, N. V.; Schoon, D.; Tranne, A. J. Orq. Chem. 1985, 50, 4231. (b) Arrieta, A.; Lecea, B.; Palomo, C. J. Chem. Soc., Perkin Trans. 1 1987, 845.

(11) Aizpurua, J. M.; Cossio, F. P.; Lecea, B.; Palomo, C. Tetrahedron Lett. 1986, 27, 4359. Doyle, T. W.; Belleau, B.; Luh, B.-Y.; Ferrari, C. F.; Cunningham, M. P. Can. J. Chem. 1977, 55, 468.

(12) Cossio, F. P.; Palomo, C. Tetrahedron Lett. 1985, 26, 4235. Idem. Ibid. 1985, 26, 4239. Haebich, D. Angew. Chem. Int. Ed. Engl. 1983, 22, 711 and references 5c, 5e, 5f and 10b of this letter.

(13) Barrett, A. G. M.; Quayle, P. J. Chem. Soc., Chem. Commun. 1981, 1076. Reider, P. J.; Grabowski, E. J. J. Tetrahedron Lett. 1982, 23, 2293. Hua, D. H.; Verma, A. Tetrahedron Lett. 1985, 26, 547.

(Received in USA 17 February 1988)