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STEREOSPECIFIC AND NON-HAZARDOUS SYNTHESES OF CIS AND TRANS-3-PHENOXYACETAMIDO-4-(2-ACETOXY-1,1-DIMETHYLETHYL)-AZETIDIN-2-ONES- KEY INTERMEDIATES FOR THE SYNTHESIS OF 6-AMIDO-1,1-DIMETHYL-CARBAPEN-2-EMS

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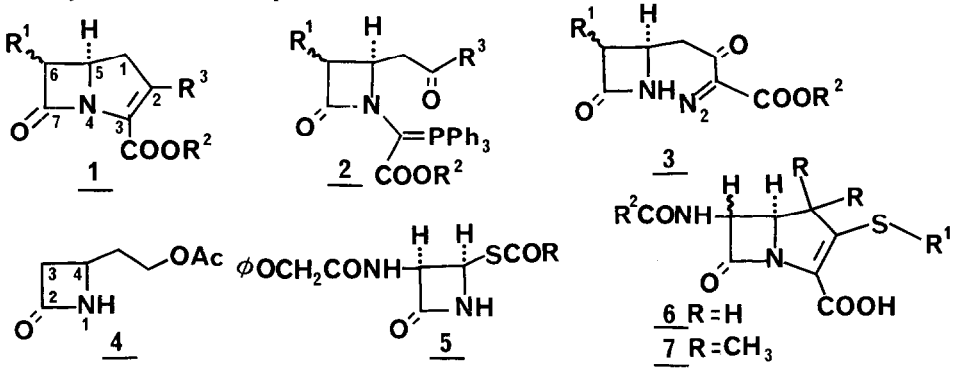
Summary: The title compounds have been prepared by a four-step sequence from 3-acetoxy-2,2-dimethyl-1-propanal and a novel non-hazardous and stereospecific route to cis-3-amido-azetidin-2-ones by the use of N-benzyl-N-carbobenzoxyglycine is described.

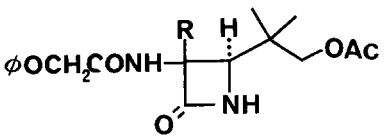
The recent discoveries of the potent antibiotics thienamycin and its relatives[1], members of the β-lactam group of antibiotics, have stimulated considerable interest in the synthesis of carbapen-2-ems of type 1 (R'=H or alkyl or substituted alkyl). Two synthetic approaches have been used successfully. One involves the formation of the C2 - C3 bond by the intramolecular Wittig reaction[2] using intermediates 2. The other requires the precursors 3 utilizing a carbene insertion reaction for formation of the C3-N4 bond[3]. Both of these routes require a N-unsubstituted azetidin-2-one as a key synthetic intermediate. For example, 4-(2-acetoxy-ethyl)-azetidin-2-one (4) was used to prepare carbapen-2-ems by the above mentioned two routes[2a,3]. 4-Acylthiazetidin-2-ones 5 derived from 6-phenoxymethylpenicillin was used by Woodward[4] to synthesize 6-amidopen-2-ems.



In contrast to the 6-alkyl-carbapen-2-ems, the 6-amido-carbapen-2-em 6 (and its dimethyl analog 7) which is a structural hybrid of thienamycin and penicillin, has received little attention. B. G. Christensen and his associates recently disclosed in a U.S. patent[5] a 24-step synthesis of the antibacterial 6. This lengthy synthesis is not stereospecific, producing mixture of cis and trans isomers at C5 and C6.

During recent research on the synthesis of β-lactam antibiotics, we wished to synthesize 6-amido-1,1-dimethyl-carbapen-2-ems 7. Cis and trans-3-phenoxyacetamido-4-(2-acetoxy-1,1-dimethylethyl)-azetidin-2-ones (8a and 8b) are key intermediates for the synthesis of 7 using a preparative procedure similar to that reported for the synthesis of carbapen-2-ems from the azetidin-2-one 4[2a,3]. 8a and 8b can also serve as synthetic intermediates for mono-bactam[6] analogs.

The synthesis of 3-amidoazetidinones normally involves an azido group as a masked amino function. The azido derivatives have been obtained by the reaction of azidoacetyl chloride or azidoacetic acid active ester derivative (prepared in situ) and triethylamine on a Schiff base. However, azidoacetyl chloride and azidoacetic acid are hazardous to use because they are prone to explosive decomposition. We now describe here the non-hazardous[7] and stereo-specific syntheses of both 8a and 8b.



8a R = αH

8b R = βH

Trans-3-amidoazetidin-2-ones:

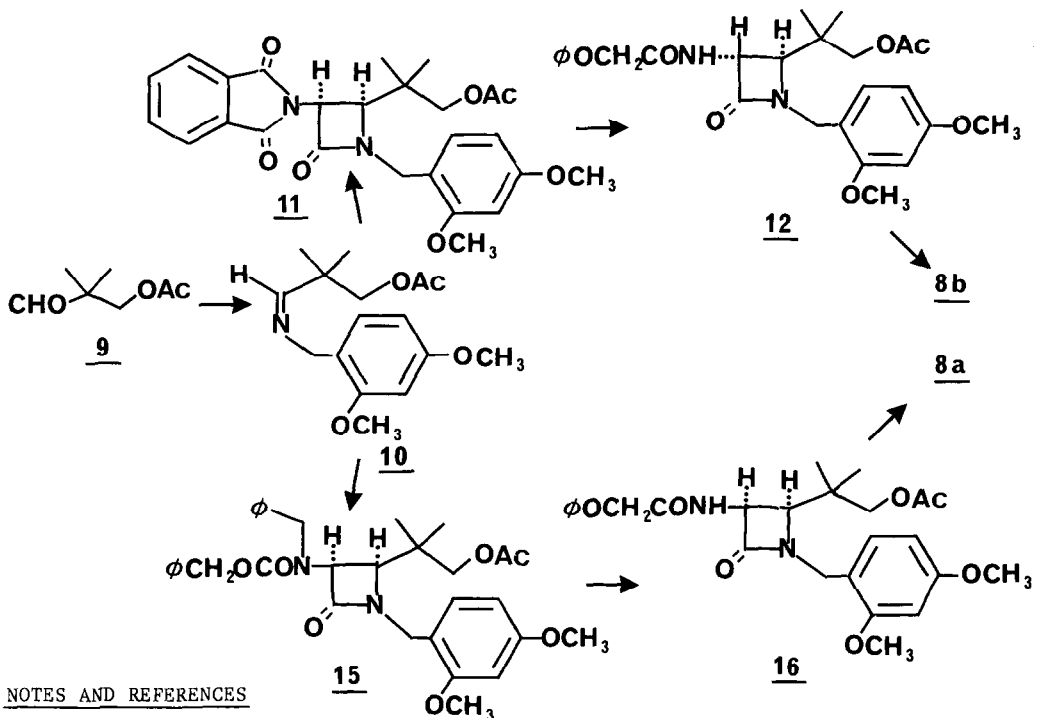
Treatment of 3-acetoxy-2,2-dimethyl-1-propanal (9)[8] with 2,4-dimethoxybenzylamine hydrochloride in the presence of triethylamine and magnesium sulfate gave the Schiff base 10[9] (each 1 mol. equiv., CH_2Cl_2, 90%). Condensation of 10 with phthaloylglycyl chloride and triethylamine yielded the 3-phthalimido-azetidinone 11 (CH_2Cl_2, r.t., 46%). The stereochemistry at C3 - C4 was confirmed to be cis by its PMR spectrum; these protons had a J value of 6 Hz, characteristic of cis disposition. Depthaloylation of 11 with anhydrous hydrazine (THF, 90°C, 1 hr) and subsequently heating with phenoxyacetylchloride (2 mol. equiv.) and triethylamine (1 ml. equiv. 90°C, 30 min.) gave the 3-amidoazetidinone 12 (60%). The configuration of this compound, however, was found to be trans at C3 - C4 having a J value of 3 Hz for these protons in its PMR spectrum. Complete epimerization at C3 had apparently occurred. Oxidation of 12 with buffered potassium persulfate[10] (4 equiv. of $K_2S_2O_8$, 2 equiv. of Na_2HPO_4 7 H_2O, 40% aqueous CH_3CN, reflux, 45 min.) afforded the trans-3-phenoxyacetamido-4-(2-acetoxy-1,1-dimethylethyl)azetidin-2-one (8b) (61%).

Cis-3-amidoazetidin-2-ones:

N-Benzyl-N-carbobenzoxyglycine ethyl ester (13) (prepared by condensation of N-benzylglycine ethyl ester with N-benzyloxycarbonyloxysuccinimide) was converted to N-benzyl-N-carbobenzoxyglycine (14) (1 mol equiv. NaOH, THF/H_2O, 98%). Formation of the N-benzyl-N-carbobenzoxyglycyl chloride in situ and subsequent reaction with the Schiff base 10 led to the synthesis of cis-β-lactam 15 (51%). (A solution of 10 mmole each of 14, $SOCl_2$ and $N(C_2H_5)_3$ in 30 ml CH_2Cl_2 was added into a solution of 10 mmole each of 10 and $N(C_2H_5)_3$ at room

temperature over 10 minutes. After an additional 30 minutes, it was washed with water and purified on silica gel column to yield pure 15). Hydrogenolysis of 15 (pretreated with RaNi, 10% Pd/C, CH_3OH, 2 hr) yielded the amino derivative which was acylated with phenoxyacetyl chloride in the presence of triethylamine (CH_2Cl_2) to give the cis-3-phenoxyacetamido-β-lactam 16 (67%). Oxidation of 16 with buffered potassium persulfate[10] afforded the cis-3-phenoxyacetamido-4-(2-acetoxy-1,1-dimethylethyl) azetidin-2-one 8a (45%).

N-Benzyl-N-carbobenzoxyglycine (13) has been used for the synthesis of other cis-3-amino-β-lactams[11] in our laboratories. Our method utilizing readily available imines and N-benzyl-N-carbobenzoxyglycine constitutes a versatile, convenient, non-hazardous and stereospecific synthesis of cis-3-amido-3-azetidin-2-ones.



NOTES AND REFERENCES

1. R.D.G. Cooper in "Topic in Antibiotic Chemistry", Vol. 3, ed. P. G. Sammes, Ellis Horwood Ltd., Chichester, 1979, p. 41.

2. a) D.B.R. Johnston, S. M. Schmitt, F. A. Bouffard and B.G. Christensen, J. Am. Chem. Soc., 100, 313 (1978). b) A.J.G. Baxter, K. H. Dickinson, P. M. Roberts, T. L. Smale and R. Southgate, J. Chem. Soc. Chem. Comm., 237 (1979). c) Roger J. Ponsford, Patricia M. Roberts and Robert Southgate, ibid, 847 (1979).

3. R. W. Ratcliffe, T. N. Salzmann and B. G. Christensen, Tetrahedron Letters, 31 (1980).

4. I. Ernest, G. Gosteli, C. W. Greengrass, N. Holick, D. E. Jackman, H. R. Pfaendler and R. B. Woodward, J. Am. Chem. Soc., 100, 8214 (1978).

5. U.S. Patent 4,218,463 (1980).

6. C. M. Cimarusti, R. B. Sykes, H. E. Applegate, D. P. Bonner, H. Brener, H. W. Chang, T. Denzel, D. M. Floyd, A. Fritz, W. H. Koster, W. Lin, W. L. Parker, M. L. Rathnum, W. A. Slusarchyk, U. Treuner and M. Young, Abstract of paper, Medicinal Division, 182nd ACS National Meeting, #4 (1981).

7. A non-hazardous synthesis of α-amido-β-lactam by the use of "Dane Salt" has been reported. Ajay K. Bose, B. Ram, S. G. Amin, Lalita Mukkavilli, John E. Vincent, and M. S. Manhas, Synthesis, 543 (1979). An one step synthesis of an α-carbamate-β-lactam has been reported. Ajay K. Bose, H.P.S. Chawla, B. Dayal and M.S. Manhas, Tetrahedron Letters, 2503 (1973); A. R. Butler, K. A. Freeman and D. E. Wright in "Recent Advances in the Chemistry of β-lactam Antibiotics", J. Elks Ed., Special Publication No. 28, The Chemical Society, London, 1977, p. 300. However, we were unable to prepare the desired monocyclic β-lactam such as 16 by this route.

8. Daniel T.W. Chu, submitted for publication.

9. Unless specified, compounds are isolated as an oil in pure form. Satisfactory spectra data (IR, MS as well as NMR) were obtained for all new compounds. Proton magnetic resonance data (δ value) taken in $CDCl_3$ are as follows:
11: 0.83 (s, 3, CH_3), 0.87 (s, 3, CH_3), 1.87 (s, 3, $COCH_3$), 3.68 (s, 2, CH_2O), 3.72 (d, J = 6, 1, C4H), 3.81 (s, 6, 2 OCH_3), 4.21 (d, J = 15, 1, 1/2 NCH_2), 4.91 (d, J = 15, 1, 1/2 NCH_2), 5.26 (d, J = 6, 1, C3H), 6.51 (m, 2, 2/3 C_6H_3), 7.22 (m, 1, 1/3 C_6H_3), 7.83 (m, 4, C_6H_4); 12: 9.34 (s, 6, 2 CH_3), 1.90 (s, 3, $COCH_3$), 3.40 (d, J = 3, 1, C4H), 3.84 (s, 8, 2 OCH_3, CH_2O), 4.14 (d, J = 15, 1, 1/2 NCH_2), 4.53 (s, 2, OCH_2CO), 4.83 (d, J = 15, 1, 1/2 NCH_2), 5.10 (dd, J = 8, J = 3, 1, C3H), 6.57 (m, 2, 2/3 C_6H_3), 7.16 (m, 7, C_6H_5, 1/3 C_6H_3, NH); 8b: 0.97 (s, 6, 2 CH_3), 2.04 (s, 3, $COCH_3$), 3.54 (d, J = 3, 1, C4H), 3.90 (s, 2, CH_2O), 4.54 (s, 2, OCH_2CO), 5.07 (dd, J = 8, J = 3, 1, C3H), 7.27 (m, s, 5, C_6H_5), 7.68 (Sb, 1, β-lactam NH), 8.20 (d, J = 8, 1, NH); 13: 1.32 (m, 3, CH_3), 3.94 (bd, 2, N-CH_2-COO), 4.26 (m, 2, CH_2), 4.62 (s, 2, N-CH_3), 5.27 (s, 2, NCOO-CH_2), 7.37 (bs, 10, 2 C_6H_5); 14: 3.96 (bd, 2, N-CH_2COO), 4.63 (s, 2, N-CH_2), 5.27 (s, 2, NCOO-CH_2), 7.36 (bs, 10, 2 C_6H_5), 9.20 (s, 1, OH); 15: 0.89 (s, 3, CH_3), 0.96 (s, 3, CH_3), 1.91 (s, 3, $COCH_3$), 3.80 (s, broad base, 9, 2 OCH_3, C4H, CH_2O), 4.04 (d, J = 15, 1, 1/2 NCH_2), 4.54 (Sb, 2, $CH_2\phi$), 4.67 (d, J = 15, 1, 1/2 NCH_2), 5.54 (db, J = 5.5, 1, C3H), 6.47 (m, 2, 2/3 C_6H_3), 7.33 (m, 11, 2 C_6H_5, 1/3 C_6H_3); 16: 0.87 (s, 6, 2 CH_3), 1.91 (s, 3, $COCH_3$), 3.57 (d, J = 5.5, 1, C4H), 3.84 (s, 8, 2 OCH_3, CH_2O), 3.97 (d, J = 15, 1, 1/2 NCH_2), 4.54 (s, 2, OCH_2CO), 4.90 (d, J = 15, 1, 1/2 NCH_2), 5.48 (dd, J = 9, J = 5.5, 1, C3H), 6.48 (m, 2, 2/3 C_6H_3), 7.10 (m, 6, C_6H_5, 1/3 C_6H_3), 7.68 (d, J = 9, 1, NH); 8a: 0.90, (s, 3, CH_3), 0.97 (s, 3, CH_3), 2.00 (s, 3, $COCH_3$), 3.66 (d, J = 5.5, 1, C4H), 3.87 (d, J = 11, 1, 1/2 CH_2O), 4.18 (d, J = 11, 1, 1/2 CH_2O), 4.71 (s, 2, OCH_2O), 5.43 (dd, J = 11, J = 5.5, 1, C3H), 7.12 (m, 7, C_6H_5, 2 NH).

10. William F. Huffman, Kenneth G. Holden, Thomas F. Buckley, III, John G. Gleason, L. Wu, J. Am. Chem. Soc., 99, 2352 (1977).

11. The synthesis of various β-lactam derivatives will be reported in subsequent papers in this journal.

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