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THE ASYMMETRIC SYNTHESIS OF β-LACTAM ANTIBIOTICS - I. APPLICATION OF CHIRAL OXAZOLIDONES IN THE STAUDINGER REACTION.

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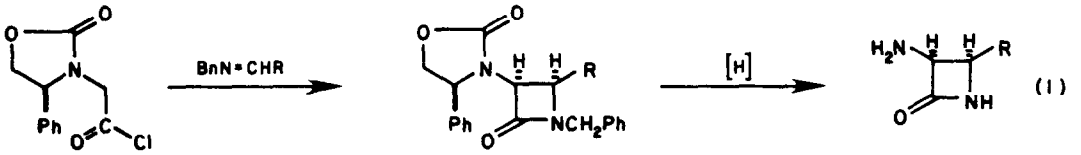
Abstract: The reactions of oxazolidone **1** with N-benzylimines proceed with exceptional levels of asymmetric induction to form the cycloadducts **2**. Subsequent dissolving metal reduction affords the homochiral β-lactam derivatives **3** in good overall yield (eq 1).

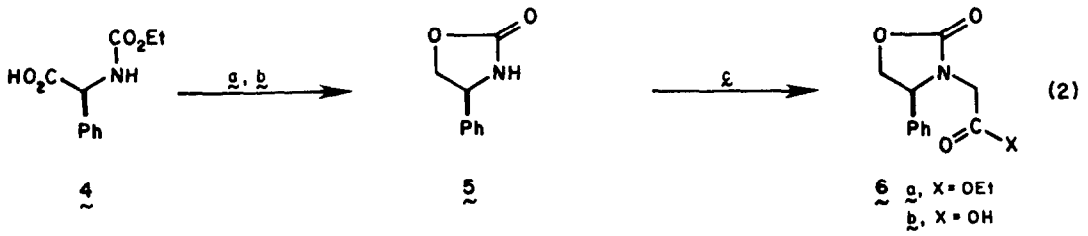
The ketene-imine cycloaddition process, frequently referred to as the Staudinger Reaction, provides the most direct access to the β-lactam nucleus.[1] When carried out with (E) imines, this reaction generally affords the cis disubstituted azetidinones with high stereoselectivity. As a consequence of the relevance of this reaction to the synthesis of β-lactam antibiotics, the establishment of absolute stereochemical control in this process stands as a worthwhile objective.[2,3] The purpose of this Letter is to outline the progress that we have achieved in the development of asymmetric ketene-imine cycloadditions employing the (4S)-phenyloxazolidylacetyl chloride (**1**) as a homochiral ketene synthon.[4] In addition to providing excellent levels of diastereoselection in the cycloaddition process, this chiral oxazolidone auxiliary may be reductively removed in a single step to give the enantiomerically pure azetidinones **3** in good overall yields (eq 1).



(1)

1 **2** **3**

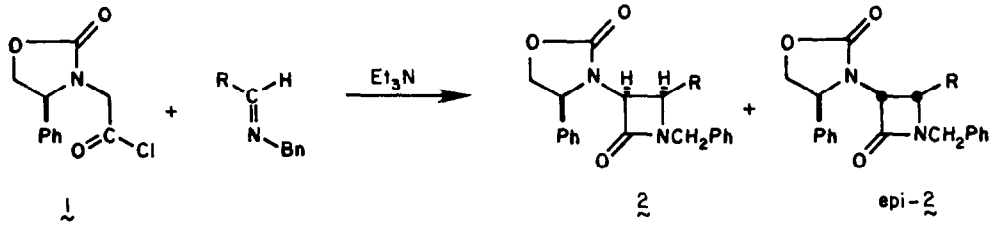
The requisite (4S)-phenyloxazolidone (**5**), $[\alpha]_D$ +49.5° (c 2.1, $CHCl_3$), mp 132-133°C, was prepared in 62% overall yield from (S)-phenylglycine as shown in Eq 2.[5] Alkylation of **5** with ethyl bromoacetate (NaH, THF, 2h, 0°C) afforded **6a** which was subjected to in situ saponification (NaOH, H_2O-THF 1h, 25°C) to provide acetic acid **6b**: mp 106-108°C; $[\alpha]_D$ +173° (c 2.0, $CHCl_3$) in 92% yield.



4 5 6 a, X = OEt b, X = OH

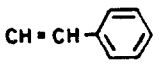
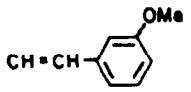
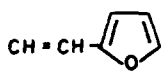
(a) $BH_3 \cdot SMe_2$, THF; (b) 0.1 equiv n-BuLi, THF, 55°C; (c) $BrCH_2CO_2Et$, NaH, 0°C; (d) NaOH, THF-H_2O, 25°C.

Transformation of carboxylic acid **6b** to the acid chloride 1 was achieved with oxalyl chloride (1.5 equiv, toluene, 3h, 60°C). This unpurified acid chloride was employed in all subsequent cycloadditions. The reactions of acid chloride 1 with the aldimines illustrated in the Table were carried out according to the following general procedure: To a 0.35 M solution of 1.0 equiv of 1 in dichloromethane, cooled to -78°C, is added 1.5 equiv of triethylamine. After 15 min a 0.65 M toluene solution of the imine (1.1 equiv) is added to the white slurry. The cooling bath is removed and the reaction is warmed to and held at 0°C for 2h. After an aqueous acid extraction and a conventional isolation procedure, the major azetidinone 2 may be readily purified by a single recrystallization of the unpurified reaction mixture. In addition, the two product diastereomers in all cases were easily separable by flash chromatography on silica gel with an average R_f difference of ca. 0.25 in CH_2Cl_2-EtOAc solvent mixtures.



1 2

Table: Cycloaddition of 1 with Representative N-Benzyl aldimines (eq 3).

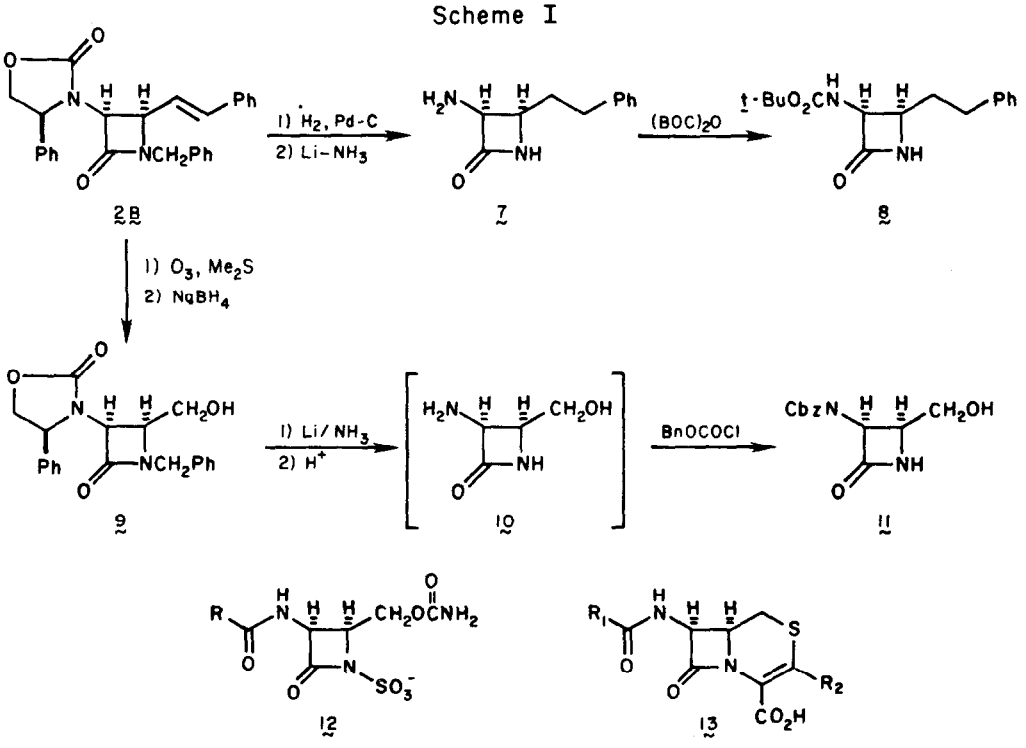
Entry	Imine (R)	2 : epi-2	Yield, % 2	mp, °C, 2
A		97 : 3	90	228-230
B		95 : 5	82	186-187
C		92 : 8	80	142-143
D		97 : 3	80	181-182

As is evident from the data provided in the Table, these reactions proceed in good yield and exhibit excellent levels of stereochemical control. In addition to providing 92-97% asymmetric induction within the cis azetidinone product manifold, these reactions appear to be devoid of trans product diastereomers.

The correlation of the stereochemical relationship between the resident asymmetric center in the chiral auxiliary and C(3) in the azetidinone **2A** ($R=C_6H_5$) was carried out in the following manner: Upon subjecting this azetidinone to dissolving metal reduction (Li, NH_3-THF, 2 min, -78°C) two significant chemical events were facilitated. First, the 4-phenyloxazolidone auxiliary was removed; second, the N-C(4) bond in the azetidinone ring was cleaved. The resulting (S)-phenylalanine benzylamide which was obtained established the absolute configuration of the major product diastereomer **2A** (R=Ph) as that illustrated. This effective method for removing the oxazolidone auxiliary was discovered only after numerous thoroughly unsuccessful attempts had been made to promote catalytic hydrogenolysis (Pd-C, H_2) of the benzylic N-C(4) bond in the oxazolidone heterocycle.[6] In fact, although hydrogenation of the double bonds in the reaction products **2B-2D** proceeded quantitatively, hydrogenolysis of either benzylic nitrogen in **2B** appeared to be subordinate to aromatic ring reduction.

Some of the more significant structural modifications that can be carried out on these cycloadducts are highlighted in Scheme I. In addition to selective hydrogenation (10% Pd-C, CH_2Cl_2), **2B** has been found to be a practical precursor to 4-hydroxymethyl β-lactams such as **9**. Ozonolysis of **2B** and subsequent borohydride reduction of the C(4) aldehyde afforded a 96% yield of **9**: mp 159-160°C, $[\alpha]_D$ +109° (c 2.2, $CHCl_3$).

Scheme I



The general protocol we have developed for the simultaneous reductive removal of the oxazolidone auxiliary and azetidinone N-debenzylation which provides access to 3-amino azetidinones such as **7** and **10** is as follows: A 0.18 M solution of the hydrogenation product derived from lactam **2B** in THF/tert-butanol (10:1) is added to a cold (-78°C) solution of 6 equiv of lithium dissolved in liquid ammonia. The volume ratio of THF/ROH to liquid ammonia is approximately 1:3. After stirring for 2 min (-78°C) the excess lithium is quenched with powdered ammonium chloride (6 equiv) and the ammonia is allowed to distill from the reaction. The residual ammonia and solvent is removed in vacuo, and the carbamate salt of **7** (or **10**) is dissolved in water and acidified briefly to pH 3 to effect carbamic acid decomposition. To isolate the free amine, a pH adjustment to 10 is followed by extraction (10% isopropanol-CH_2Cl_2) to give the 3-aminoazetidinone **7** which can be subsequently transformed to **8** with tert-butyl pyrocarbonate in 84% overall yield from **2B**. When dealing with highly water soluble intermediates such as amino azetidinone **10**, in situ amine derivatization has been found to be most expedient. In this case, after the decomposition of the carbamic acid at pH 3, the solution is adjusted to and maintained at pH 8 and treated with benzyl chloroformate (3 equiv, 3h, 25°C) to give **11** (62%) as a crystalline solid: mp 128.5-129.5°C; $[\alpha]_D$ +8.6 (c 0.9, $CHCl_3$). This azetidinone has also been independently prepared by Hoffmann-LaRoche in conjunction with the synthesis of their monobactam Ro 17-2301 (12).[7] Racemic azetidinones closely related to **11** have also been employed in the synthesis of cephalosporin analogs such as **13**.[8,9]

In summary, the application of 4-phenyloxazolidylacetyl chloride (**1**) in the Staudinger reaction (eq 3) provides an effective route to homochiral cis fused azetidinones. The subsequent one-step deprotection of these cycloadducts renders this ketene-imine cycloaddition sequence very competitive with even racemic reactions of this type. We are currently applying this methodology to the asymmetric synthesis of nontraditional β-lactam antibiotics. One such study is described in the following Letter.[10]

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References and Notes

1. For a review, see Holden, K.G. in "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R.B. and Gorman, M., Eds; Academic Press: New York, 1982; Vol 2, Chapter 2.
2. For a recent review see Labia, R.,; Morin, C. J. Antibiotics **1984**, 37, 1103-1129.
3. Hubschwerlen, C.; Schmid, G. Helv. Chim. Acta **1983**, 66, 2206-2209.
4. During the course of this research a related ketene-imine cycloaddition has been reported: Ikota, N.; Hanaki, A. Heterocycles **1984**, 22, 2227.
5. Pirkle, W.H.; Simmons, K.A. J. Org. Chem. **1983**, 48, 2520 and references cited therein.
6. For a related system which afforded similar problems in hydrogenolysis see: Mukaiyama, T.; Iwasawa, N. Chemistry Lett. **1981**, 29-32.
7. Wei, C-C.; Tengi, J.; Weigele, M.; presented at the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, Nevada, Octover 1983 (poster session). We thank Dr. Dennis Keith for data on this compound.
8. Huffman, W.F.; Holden, K.G.; Buckley, T.F., III; Gleason, J.G.; Wu, L. J. Am. Chem. Soc. **1977**, 99, 2352-2353.
9. Bryan, D.B.; Hall, R.F.; Holden, K.G.; Huffman, W.F.; Gleason, J.G. J. Am. Chem. Soc. **1977**, 99, 2353-2355.
10. Evans, D.A.; Sjogren, E.B. Tetrahedron Lett. **1985**, accompanying communication.

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