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A CONVENIENT ROUTE TO AZETIDINE-2,3-DIONES AND CIS-3β-AMIDO AZETIDINONES

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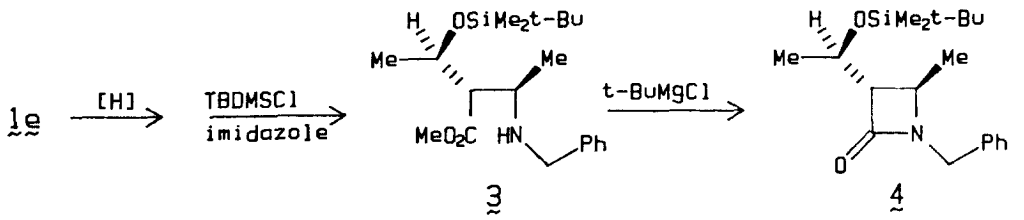
Abstract: The synthesis of 3β-amido azetidinones, **8a** and **8b**, via azetidine-2,3-diones is described.

For some time, there has been a major emphasis on the synthesis of bicyclic β-lactams such as penicillin, cephalosporin, and recently, thienamycin.[1] The discovery of a new generation of β-lactam antibiotics including nocardicin-A and the monobactams[2] has evoked an intense interest.[3] Previously, we were able to demonstrate the importance of nitrones in the synthesis of a thienamycin model.[4] Herein, we focus our attention not only on the synthesis of the parent β-lactam nucleus, but also on the conversion of the hydroxyethyl functionality to the requisite 3-amido substituent. This methodology provides the basis for an entry into diverse classes of penicillins, cephalosporins, and nocardicins.

The key to the formation of the 3β-amido azetidinones lies in the accessibility of the requisite monocyclic 3-hydroxyethyl precursor. Such compounds were obtained by an intramolecular [3+2]-cycloaddition methodology developed by us previously.[4] The reaction of C-methyl-N-benzylnitrone with methyl crotonate affords isoxazolidine **1e** (90%) efficiently (cf. Table 1). This compound derives either by passage through an exo-transition state, or the corresponding endo-transition state after a prior E ⟶ Z isomerization.[5] The initial stereochemical assignment was made tentatively by comparison of the NMR spectrum of **1e** (J_{34} = 8.5 Hz; J_{45} = 9.0 Hz) with those of similar isoxazolidines reported previously.[6] While the exclusive formation of **1e** (rather than **2e**) is surprising, it should be noted that N-alkyl nitrones tend to give more exo-adduct than their N-arylated counterparts,[6] in accord with our results.

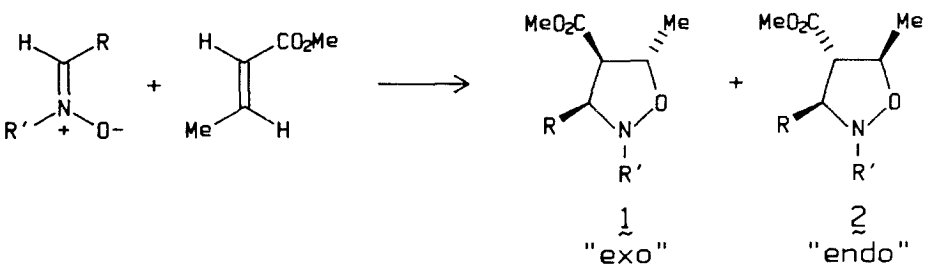
We have demonstrated that isoxazolidine **1e** gives, after hydrogenolysis (Zn/acetic acid), selective masking of the secondary hydroxyl group (TBDMSCl/imidazole),[7] and ring closure through the agency of t-butylmagnesium chloride, the monocyclic t-butylsiloxy β-lactam **4** in 85% yield. The IR spectrum (neat) does not indicate absorption in the 2-3 μm spectral region, but does



indicate the presence of an intense carbonyl absorption (5.76 μm). The PMR spectrum displays the expected doublets at δ 1.13 and 1.18 ppm attributable to the C-4 and C-5 bound methyl groups. In addition, a doublet of doublets at δ 2.85 ppm (1H, J = 1.5 Hz, H_3) suggests a trans-relationship for the protons at C-3 and C-4. We have been unable to detect the presence of any other stereoisomers corresponding to 4. This finding not only supports the highly stereoselective and regioselective nature of the nitrone cycloaddition to methyl crotonate, but also suggest that the product isoxazolidine retains the stereochemistry depicted, a consequence which is consistent with an exo-addition process. We now believe that β-lactams with cis-related substituents at C-3 and C-4 can not be readily formed by the application of the Grignard methodology. This is reflected in the experimental findings shown in Table 1 which suggest that only the "exo" adducts are readily converted to β-lactams. It should be noted that the transition states for closure of the amino esters derived from the "endo" adducts (i.e. which would lead to a cis-arrangement of substituents at C-3 and C-4) experience appreciable steric congestion.

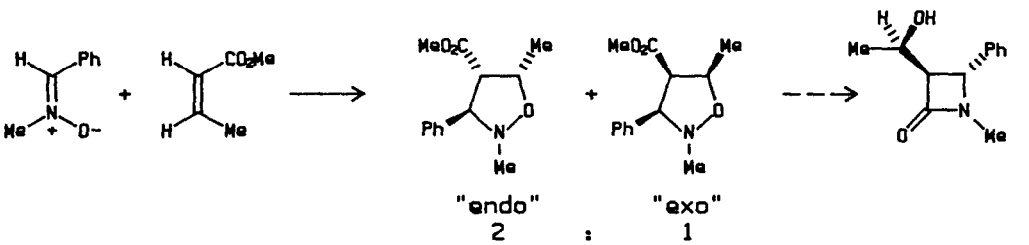
Table 1

Conversion of Isoxazolidines to β-Lactams



	R	R'	endo/exo	% conversion to β-lactam
a	Ph	Ph	87/13	0
b	Ph	Me	50/50	50
c	Me_2CH	Ph	100/0	0
d	Me_2CH	CH_2Ph	33/67	60
e	Me	CH_2Ph	0/100	100

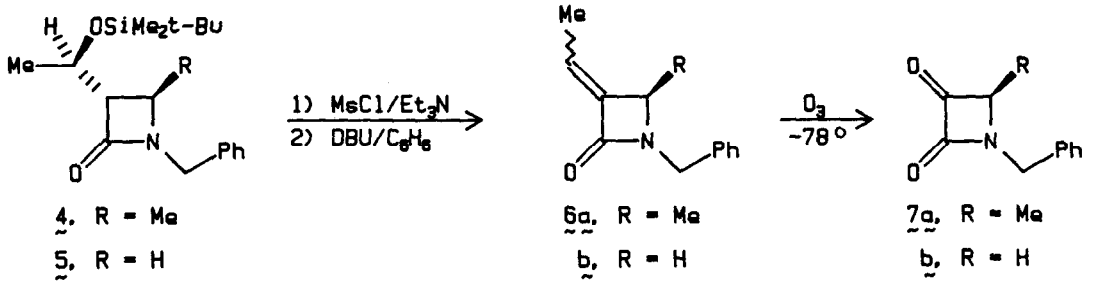
We have taken the 50/50 mixture of isoxazolidines derived from C-phenyl-N-methylnitrone (Table 1; entry b) and subjected it to hydrogenolysis (Zn/HOAc) and selective O-blocking (TBDMSCl/imidazole) conditions. The silyl ethers were then separated chromatographically and exposed to the conditions of the closure reaction (i.e. t-butylmagnesium chloride). Only one of the isomers could be induced to close to a β-lactam under these conditions (i.e. presumably the compound derived from the "endo" isomer would not close). Moreover, C-phenyl-N-methylnitrone was allowed to react with methyl cis-crotonate to give a 2:1 mixture of "endo" and "exo" adducts, respectively. The stereochemical assignments are based on firm NMR evidence.[6] The adducts could



be chromatographically separated, and attempts were made to convert each to the β-lactam. Only the "exo" isomer could be transformed into the β-lactam under the conditions of the Grignard procedure. Thus, it appears that the stereochemistry of the starting isoxazolidines can be assigned with some assurance by application of this technique.

The 4-unsubstituted β-lactam 5 (R = H) was prepared following the same sequence of reactions as noted above. The final closure proceeded in 90% yield.

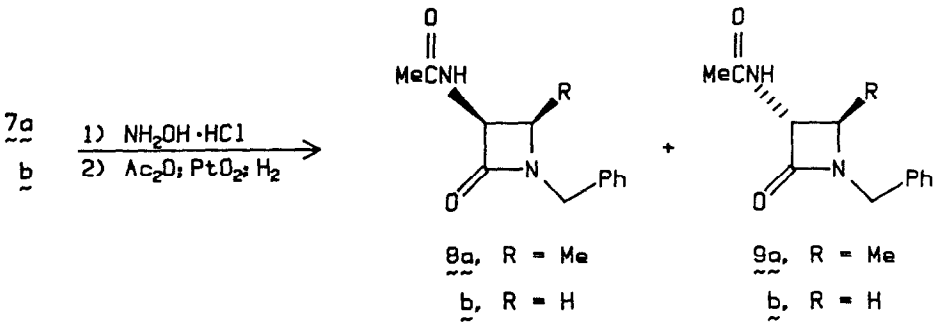
Treatment of β-lactams 4 and 5 with methanesulfonyl chloride, followed by elimination of the mesylate grouping with DBU in benzene, gave the ethylidene β-lactams, 6a and 6b, in 67% and 85% yield, respectively. Ozonolysis of either 6a or 6b furnished the corresponding azetidine-2,3-diones, 7a and 7b, in 70-80% yield. The IR spectrum ($CHCl_3$) of 7a revealed the presence of two carbonyl absorptions at 5.60 and 5.71 μm. The PMR spectrum of 7a revealed the presence of methyl doublet δ 1.25 ppm and a quartet at δ 3.93 ppm due to the proton at C-4.



4. R = Me
5. R = H

6a. R = Me
b. R = H

7a. R = Me
b. R = H



The PMR spectrum of **7b** compared well with that reported by Ban and co-workers.[8] Exposure of **7a** to an oximation procedure, followed by reductive acetylation (H_2; PtO_2; Ac_2O) afforded a mixture of cis- and trans-3-aminoacetyl β-lactams, **8a** and **9a** (R = Me), in a 5:1 ratio (59% yield). The same overall strategy produced **8b** in 42% yield from **7b**.

Reductive amination ($NaBH_3CN/NH_4Br$)[9] of **7a**, followed by the acetylation of the resulting amine, gave **8a** and **9a** (50%) in a 2:1 ratio.

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