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β-LACTAM SYNTHESIS: CYCLIZATION VERSUS 1,2-ACYL MIGRATION-CYCLIZATION. THE MECHANISM OF THE 1,2-ACYL MIGRATION-CYCLIZATION

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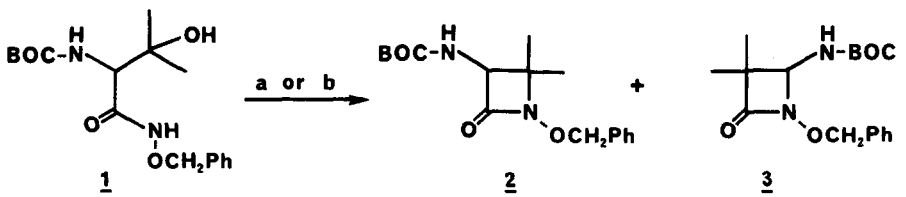
Abstract: The cyclization of hydroxamate 1 unexpectedly afforded two isomeric β-lactams 2 and 3. The mechanism for the formation of 3 has been shown by carbon-13 labeling to involve a novel 1,2-acyl migration-cyclization process.

In the preceeding paper[1] we described the cyclization of hydroxamate 1 to give the desired azetidinone 2 and also, quite unexpectedly, the isomeric azetidinone 3 in approximately a 2:1 ratio, respectively (Scheme 1). With increasing effort being directed toward the synthesis of novel monocyclic β-lactams for antimicrobial evaluation, we felt that determination of the mechanism responsible for the formation of 3 would allow the design of better substrates and/or reaction conditions. In this communication we wish to report elucidation of the mechanism for formation of 3 utilizing carbon-13 labeling.[2]

Scheme 1

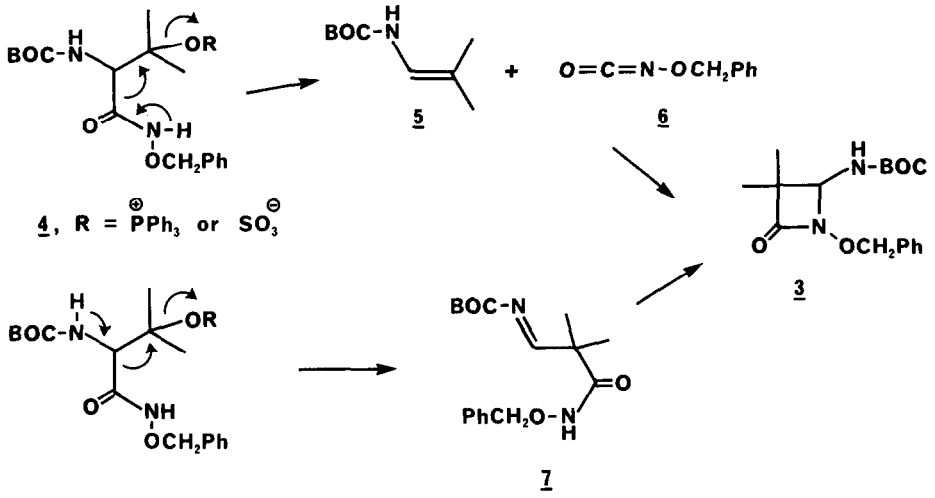


a) 2-picoline · SO_3, MIBK; $K_2B_4O_7$, aq. KOH, 70°C; 2:3, 2:1. b) Ph_3P, CCl_4, Et_3N, CH_3CN, 35°C; 2:3, 1:1

In principle, the activated hydroxamates 4 could undergo heterolytic fragmentation to yield olefin 5 and isocyanate 6 which upon 2+2 cycloaddition[3] should afford 3 (Scheme 2). This fragmentation process is analogous to the fragmentation of a β-hydroxy acid to yield CO_2, H_2O, and an olefin.[4] Alternatively, a 1,2-shift of the hydroxamate moiety with its bonding electrons and concomitant displacement of triphenylphosphine oxide or sulfate ion should afford imine 7 after proton loss from the BOC-amino group. Subsequent ring closure should then yield 3.

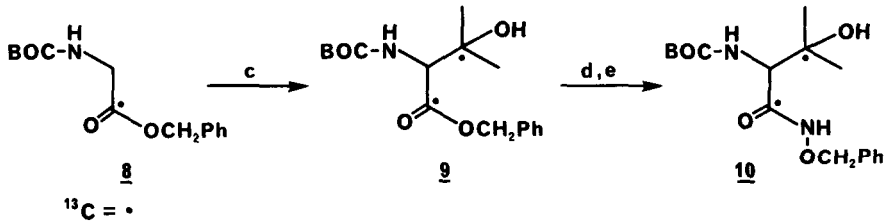
The 1,2-migration of electon withdrawing groups to electron deficient centers has been observed in numerous carbenium ion rearrangements.[5] In addition, the migration of COO^- has been shown to occur in benzilic acid[6] and tertiary ketol[7] rearrangements. However, the 1,2-migration of electron withdrawing groups with simultaneous expulsion of a leaving group remain relatively rare.[8]

Scheme 2



In order to determine whether 3 is formed by an intermolecular fragmentation-recombination or intramolecular 1,2-acyl migration-cyclization process, we performed a crossover experiment using a 1:1 mixture of doubly ^{13}C labeled (10) and unlabeled (1) hydroxamate. The required doubly labeled hydroxamate 10 was prepared as shown in Scheme 3 using glycine-1-^{13}C and acetone-2-^{13}C.[9] Glycine-1-^{13}C was converted to N-BOC-glycine-1-^{13}C benzyl ester 8 in 86% yield by treatment with BOC-ON and Et_3N in aqueous acetone[10] followed by esterification with benzyl bromide and $KHCO_3$ in DMF.[11] Generation of the dianion of 8 with LDA in THF, followed by the addition of acetone-2-^{13}C, afforded the doubly labeled aldol product 9 in 77% yield.[12] Hydrogenolysis of the benzyl ester of 9 followed by DCC/HOBT mediated coupling with O-benzylhydroxylamine afforded the desired labeled hydroxamate 10.

Scheme 3

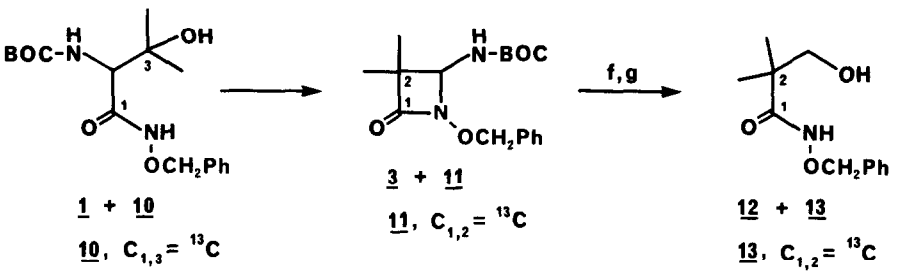


c) LDA, THF, -78°C; acetone-2-^{13}C; HOAc; d) H_2, $Pd(OH)_2/C$, EtOH; e) DCC, HOBT, EtOAc; H_2NOCH_2Ph

Treatment of an equimolar mixture of unlabeled and labeled hydroxamates 1 and 10, respectively, with 2-picoline · SO_3 in methyl isobutyl ketone (MIBK) afforded the corresponding mixture of O-sulfates.

Subsequent cyclization by the addition of water and $K_2B_4O_7$ (4 equiv.) and warming to 70°C followed by the addition of 2 equivalents of KOH over 45 min afforded the expected mixture of β-lactams 2 and 3 after conventional workup. Recrystallization from isopropyl ether to remove most of 2, followed by careful chromatography (Flash, silica gel; THF:CH_2Cl_2, 3:97), afforded a mixture of the unlabeled and labeled isomeric β-lactams 3 and 11 (Scheme 4). Unfortunately, this material was contaminated with a trace amount of an impurity which interfered with the detection of a small amount of label crossover by ^{13}C NMR. The instability of 3 towards repeated chromatography prevented rigorous purification; therefore, the mixture of 3 and 11 was converted[1] to the corresponding mixture of alcohols 12 and 13 which was easily purified.

Scheme 4



f) CH_3CN, H_2O, conc. HCl; g) $NaBH_4$, H_2O, THF

The ^{13}C NMR of the mixture of 12 and 13 revealed enriched carbon atoms at 42.65 and 175.29 ppm which were split into doublets by direct ^{13}C-^{13}C coupling (J = 48.2 Hz)[13]. This coupling clearly indicates that the ^{13}C labels are now adjacent whereas in starting hydroxamate 10 the labels were in a 1,3-relationship. In addition, there was no increase in the amount of monolabeled product by ^{13}C NMR (detectable as a singlet between the doublets due to adjacent ^{13}C atoms) or by mass spectral analysis. We therefore conclude that formation of 3 from hydroxamate 1 involves an intramolecular rearrangement followed by subsequent ring closure as depicted in Scheme 2[14].

Cyclization of 1 using Mitsunobu conditions[15] ($Ph_3P/CCl_4/Et_3N$ in CH_3CN) afforded a nearly equal mixture of 2 and 3[16] whereas the use of the tandem sulfation-cyclization procedure afforded a 2:1 mixture of 2 and 3, respectively. We interpret this observation to suggest that the relative amount of desired cyclization *vs.* rearrangement is dependent upon the leaving group. The better leaving group (triphenylphosphine oxide) appears to impart more S_N1-like character to the reaction and thus more rearrangement is observed. One could reasonably expect then that a poorer leaving group should have a beneficial influence on the ratio of cyclization *vs.* rearrangement.

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References and notes:

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13. ^{13}C NMR: 12, (67.8 MHz, $CDCl_3$) δ 175.29, 135.25, 129.28, 128.72, 128.53, 77.97, 69.18, 42.65, 22.28.
14. However, this experiment does not rule out the possibility of a solvent caged fragmentation-recombination pathway which we consider to be very unlikely.
15. For the use of the Mitsunobu reaction to prepare β-lactams from substituted hydroxamates, see M. J. Miller, P. G. Mattingly, M. A. Morrison, and J. F. Kerwin, Jr., *J. Am. Chem. Soc.*, **1980**, *102*, 7026.
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