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A NEW SYNTHESIS OF β-LACTAMS. OXYGENATION OF DIANIONS OF AZETIDINE CARBOXYLIC ACIDS

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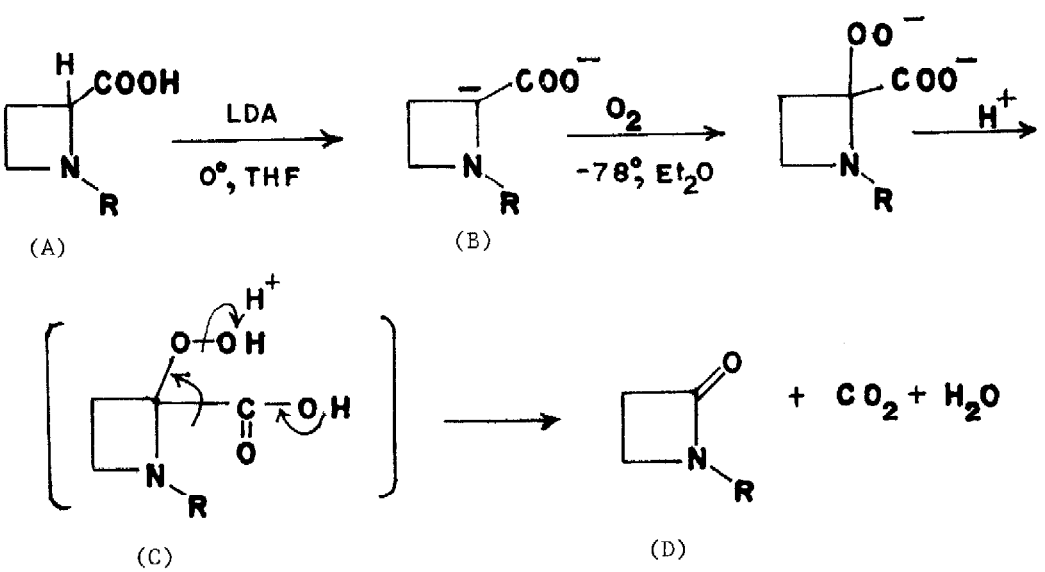
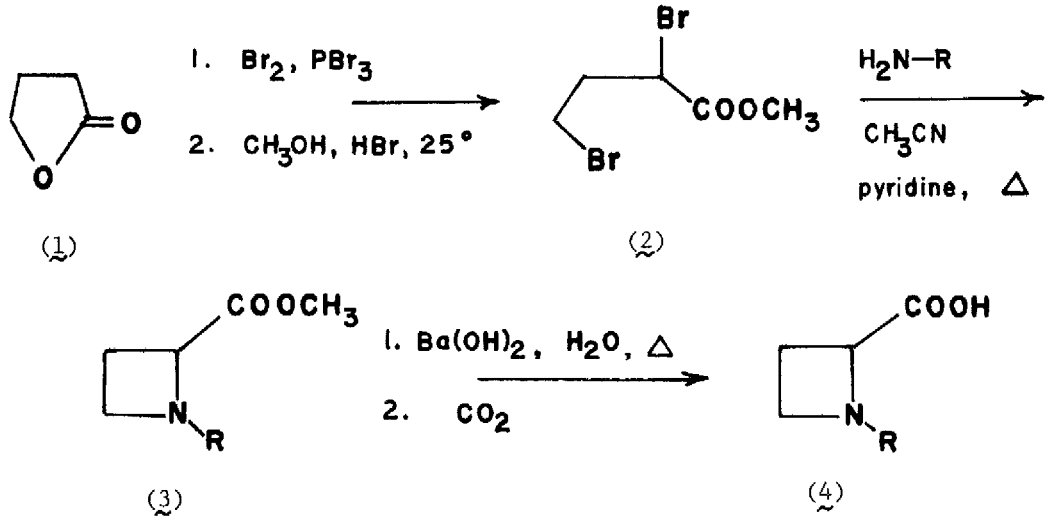
The importance of the penicillins and cephalosporins among medicinal agents has continued to stimulate studies on the chemistry of β-lactams.[1] New methods of constructing the four-membered lactam ring are of particular interest in connection with the synthesis of analogues of the naturally occurring antibiotics.[2] In this report we describe a novel procedure for the preparation of β-lactams which utilizes readily available starting materials and has considerable flexibility in the types of substituents incorporated.

The key feature of the synthetic method involves the oxidative decarboxylation of an azetidine carboxylic acid (A) by oxygenation of the dianion (B) formed at low temperature from reaction with two equivalents of lithium diisopropylamide (LDA). Uptake of oxygen by (B) yields the dilithium salt of the hydroperoxy acid (C) which, upon acidification, rapidly decomposes to the β-lactam (D).



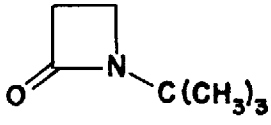
For this study we have modified[3] the procedure reported by Cromwell[4] for the preparation of azetidine carboxylic acids from γ-lactones. For example, starting with γ-butyrolactone (1), the simple sequence of steps outlined in Scheme I provides a variety of azetidine carboxylic acids for the oxidative transformations described below.

Scheme I

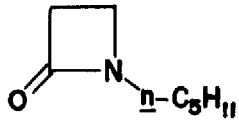


The oxidative decarboxylation sequence was carried out in a manner similar to that described in our earlier report.[6] Thus, treatment of the azetidine carboxylic acid[7] (4) with 2.2 equivalents of LDA at 0° for 1 hr gave an orange-yellow solution of the dianion (B). The dianion, cooled to -78° was added *via* syringe to a reaction well[8] containing Et_2O at -78° into which dry oxygen was continuously circulated.[9] After uptake of one equivalent of oxygen (*ca.* 1 min), the reaction mixture was treated with 2.3 equivalents of a *p*-toluenesulfonic acid - THF solution (dropwise addition) at -78°.[9] After the mixture had warmed to room temperature, it was filtered free of all salts, concentrated *in vacuo*, diluted with dry Et_2O and filtered again. Drying ($MgSO_4$) followed by removal of solvent and column chromatography (neutral alumina, $CHCl_3$-Et_2O) afforded the β-lactams[10] in yields ranging from 50-61% which could be further purified by kugelrohr distillation.[11]

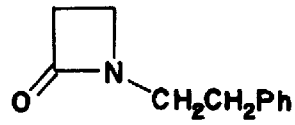
β-Lactams prepared by the above method are shown below. These compounds (all of which exhibit infrared absorption at 1745-1740 cm^{-1}) were further characterized by comparison (ir and nmr spectra) with authentic samples, or, in the case of new compounds, by ir, nmr, mass spectrometry and elemental analyses.



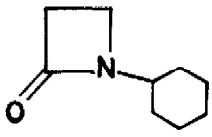
nmr($CDCl_3$): δ 3.18 (t,2H)
2.77 (t,2H)
1.33 (s,9H)



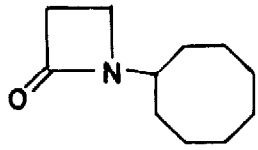
δ 3.13 (m,4H)
2.84 (t,2H)
1.32 (m,6H)
0.88 (t,3H)



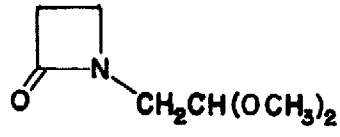
δ 7.27 (m,5H)
3.44 (t,2H)
3.04 (t,2H)
2.82 (m,4H)



δ 3.43 (s,br,1H)
3.21 (t,2H)
2.83 (t,2H)
1.50 (m,10H)



δ 3.75 (s,br,1H)
3.19 (t,2H)
2.80 (t,2H)
1.65 (m,14H)



δ 4.47 (t,1H)
3.38 (s,6H)
3.36 (t,2H)
3.33 (d,2H)
2.95 (t,2H)

We are investigating the application of this method of β-lactam formation to the synthesis of compounds related to the penicillins and cephalosporins as well as to the preparation of other natural products containing the β-lactam ring.

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References and Notes

1. M.S. Manhas and A.K. Bose in "Synthesis of Penicillin, Cephalosporin C and Analogs," Wiley Interscience, 1969; and "Beta-Lactams Natural and Synthetic" part 1 (1971), Wiley Interscience.

2. For recent synthetic studies, see B.G. Christensen, et al, Tetrahedron Lett., 3567(1974); J. Amer. Chem. Soc., 96, 7582, 7584(1974), J.E. Baldwin, et al, J. Amer. Chem. Soc., 97, 5957(1975); P.W. Wojtkowski, et al, J. Amer. Chem. Soc., 97, 5628(1975); T. Kamiya, et al, J. Amer. Chem. Soc., 97, 5020(1975).

3. We have found that the following modifications result in significantly improved yields of azetidine carboxylic esters compared with the literature procedure:[4] (a) use of pyridine as cosolvent (5:3 CH_3CN: pyridine); (b) lower temperatures (ca. 55°); (c) shorter reaction times (6 hr); (d) use of Et_2O as the extraction solvent followed directly by distillation.

4. N.H. Cromwell and R.M. Rodebaugh, J. Heterocyclic Chem., 6, 435(1969).

5. Formation of (3) from (2) most probably involves displacement of the α-halogen as a first step, followed by an intramolecular cyclization. If displacement of the primary bromine took place initially, substantial γ-lactam formation might be expected as a competing reaction. Under the conditions used, the γ-lactam was a minor side-product.

6. H.H. Wasserman and B.H. Lipshutz, Tetrahedron Lett., 4611(1975).

7. The crystalline amino acid was added in one batch. Reactions were run on a 3-5 mmole scale.

8. C.S. Foote and R.S. Vickers, Boll. Chim. Farm., 109, 599(1970).

9. The decarboxylation appeared to take place immediately upon neutralization at -78° as evidenced by the increase in the volume of gas stored in the buret of the oxygenation apparatus.[8]

10. The purity of the β-lactam at this stage was on the order of 90-99% as shown by nmr and/or glc.

11. Kugelrohr distillation (employed to obtain analytically pure products) results in substantial decomposition of the β-lactam.