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FREE RADICAL CYCLIZATIONS LEADING TO FOUR-MEMBERED RINGS. I. BETA-LACTAM PRODUCTION USING TRIBUTYLTIN HYDRIDE

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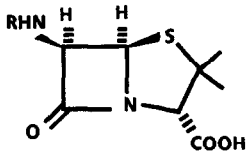
Abstract: Use of $HSnBu_3$ for the reductive cyclization of suitable enamides having a bromide substituent alpha to the carbonyl group affords beta-lactams in good yields.

Medicinal chemists have long exploited the extraordinary level of anti-microbial activity found in the penicillin 1 (1) and cephalosporin 2 (2) families of beta-lactams. Of particular importance is the unique ability of beta-lactams to interfere with bacterial cell wall biosynthesis (3). Beta-lactams exhibit a high therapeutic index in both humans and livestock and the capability of undergoing rational modification in biological activity by systematic alteration in the molecular structure of fermentation-derived prototypes (4). The need to achieve more satisfactory activity against Gram-negative bacteria and the evolution of genetically transferable drug resistance have spurred important recent develop-ments such as the biological evaluation and total synthesis of unusual beta-lactams (*e.g.* thienamycin 3 (5)).



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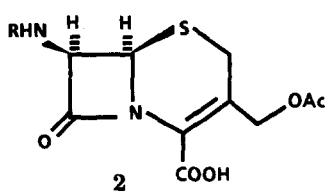

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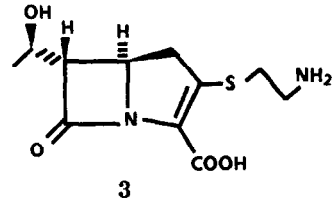

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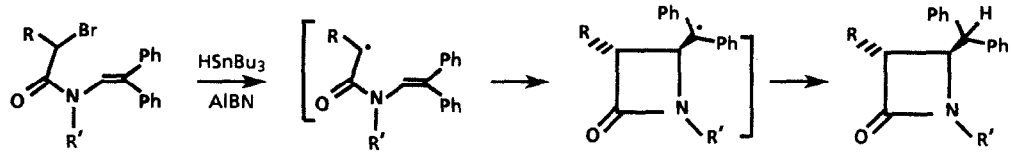
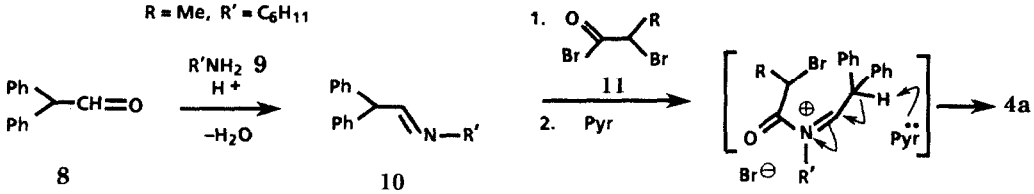
Known synthetic strategies for the creation of beta-lactam antibiotics range from the classical DCC dehydration of a suitable amino acid precursor (6) to unusual [2+2] cycloadditions employing chlorosulphonyl isocyanate (7). However, except for rare examples (such as Pattenden's work in which 4-exo-trig cyclization of radicals derived from a carbamyl cobalt salophen intermediate is proposed (8)), free radical cyclization chemistry (9) has played a minimal role in beta-lactam synthetic methodology as well as in approaches to 4-membered rings in general. Given the successful transformation of alpha-bromo allylic esters into 2,3-disubstituted butyrolactones (10), could an analogous transformation provide a 4-membered heterocycle? To test the feasibility of this approach, we sought to convert the simple diphenyl-substituted enamides 4 into 7 via the intermediacy of radicals 5 and 6 wherein it was postulated that formation of the highly stabilized benzhydryl radical 6 would favor the cyclization pathway.



4 5 6 7

a R = Me, R' = C_6H_{11}
b R = Et, R' = C_6H_{11}
c R = Et, R' = $C(CH_3)_3$
d R = Et, R' = Me

Condensation of diphenylacetaldehyde 8 with primary amine 9 under acid-catalysis gives imine 10 (12). Without further purification, imine 10 is mixed with alpha-bromo acid halide 11 and an excess of pyridine to afford an iminium salt 12 that then undergoes loss of HBr with concomitant double bond isomerization to form the desired enamide 4a (13). Similarly, additional enamide analogs (4b, ..., 4d) were prepared. Yields (11) varied as follows: 4a =93%; 4b = 97%; 4c = 49%; 4d = 55%. Preparation of the N-Me enamide 4d required the use of anhydrous magnesium sulfate as both Lewis acid catalyst and dehydrating agent during imine formation.



8 10 12

Slow addition of a benzene solution containing tributyltin hydride (1.0 equiv.) and AIBN (0.1 equiv.) to a solution of enamide 4a in refluxing benzene followed by further heating and a standard non-aqueous work-up (14) with ligroin and acetonitrile affords a crude reaction product that, by proton NMR, is nearly pure beta-lactam 7a. While a few percent of both tributyltin bromide and the corresponding debromination product 13a were present as contaminants, no enamide starting material 4a was detectable. Simple trituration plus recrystallization gives pure beta-lactam 7a. Analogously, enamides 4b, 4c, and 4d also were converted into the corresponding beta-lactams in the following yields (11): 7a = 69%; 7b = 70%; 7c = 58%; 7d = 40%. Somewhat surprisingly, with the N-Me enamide 4d, a significant amount (ca. 60%) of debromination product 13d formed. We speculate that bulky substituents on the nitrogen atom may facilitate cyclization.

13 14

Although proton NMR data, the lactam carbonyl IR shifts (1726-1747 cm^{-1}) (15) and mass spectroscopic evidence were consistent with the proposed beta-lactam structures **7a**, ..., **7d**, we were cautious in accepting this interpretation. Successful completion of a single-crystal X-ray study (16) performed on **7a** removed any remaining uncertainty as to the identity of these putative beta-lactam products. Furthermore, for the three most readily isolable beta-lactams (*e.g.* **7a**, **7b**, and **7c**), TLC and NMR examination of both the purified products and the mother liquors are consistent with only a single diastereoisomer being formed during the cyclization process.

On-going work involves replacement of the two phenyl rings in the precursor enamides by more synthetically useful radical stabilizing groups such as the bis(carboalkoxy) analog **14** to be followed by attempted beta-lactam formation. Also underway are attempts to employ similar chemistry for the generation of substituted cyclobutanes.

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11. All new compounds exhibited satsifactory chromatographic and analytical properties. For brevity, only selected data are included in this paper.
12. Diphenylacetaldehyde (1.07 g; 5.44 mmol), benzene (50mL), cyclohexylamine (0.57 g; 5.74 mmol), and pTsOH (0.062 g; 0.3 mmol) were deaerated and then refluxed together under nitrogen using a Dean-Stark apparatus to remove water. After cooling to RT, an aliquot was taken for NMR analysis. Based on NMR, the crude imine is obtained in nearly 100% yield. This air- and moisture-sensitive material was used as is for the acylation without further treatment: characteristic NMR signals at δ = 6.6 (brs, 1H), 3.75 (brs, 1H).
13. The crude imine (ca. 5.44 mmol) in benzene was cooled to 0°C. Addition of 2-bromopropionyl bromide (0.68 mL; 6.49 mmol) was followed by 30 min stirring. Pyridine (1.30 mL; 16.1 mmol) was added to the resulting suspension. After stirring at RT for 16 hrs, the rxn. mixture was diluted with ether, washed with water and brine, dried, and the volatiles removed to give an amber syrup that slowly crystallized. Flash filtration (17 g silica gel: elution with ligroin followed by $CHCl_3$) gave spectroscopically pure **4a** as a colorless oil that crystallized on standing under ligroin (mp 120-121°C: 2.09g: 93%). IR ($CHCl_3$) υ = 1653 cm^{-1}: ^1H NMR δ 7.4-7.2 (m, 10H), 6.39 (s, 1H), 4.7 (q, 1H, J = 6.6 Hz), 4.45-4.3 (m, 1H), 2.1-1.0 (m, 13 H including 1.17 (d, J = 6.6 Hz, 3H)): ^{13}C NMR 168.89.
14. To a refluxing benzene solution (80 mL) of enamide **7a** (0.824 g; 2 mmol) was added (via syringe-pump over 3 hrs) a solution of tributyltin hydride (0.55 mL; 2 mmol), AIBN (0.042 g; 0.26 mmol), and benzene (25 mL). After an additional 13 hrs. at reflux, the solution was cooled to RT, evaporated to a yellow oil, taken up in acetonitrile (80 mL) and then washed with 5 x 15 mL of ligroin to remove most organotin by-products. Evaporation of the acetonitrile solution afforded a colorless oil. Trituration of this oil with ligroin produced a white, crystalline spectroscopically pure sample of **7a** (0.459 g: 69 %). Slow recrystallization from CCl_4 gave crystals (mp 117-117.5°C) suitable for X-ray. IR ($CDCl_3$) υ = 1728 cm^{-1}: ^1H NMR ($CDCl_3$) δ 7.45-7.15 (m, 10H), 4.0 (dd, J = 2.1, 9.9 Hz, 1H), 3.9 (d, J = 9.9 Hz, 1H), 2.7-2.55 (dq, J = 2.1, 7.5 Hz, 1H), 2.5-2.35 (m, 1H), 1.75-0.7 (m, 13 H including 1.12 (d, J = 7.2 Hz, 3H)): ^{13}C NMR 170.79.
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16. Ho, Douglas, unpublished results, Department of Chemistry, University of Cincinnati, 1990. Space Group Cc (No. 9). Structure solved by direct methods (XS: TREF) with refinement by full matrix least squares (XLS). (Final R(F) = 0.0616; wR(F) = 0.0789). All bond angles and bond distances are as expected. Complete details available on request to JLB.

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