ENAMINE-SINGLET OXYGEN REACTIONS. SYNTHESIS OF β-LACTAMS FROM ESTERS OF AZETIDINE CARBOXYLIC ACIDS

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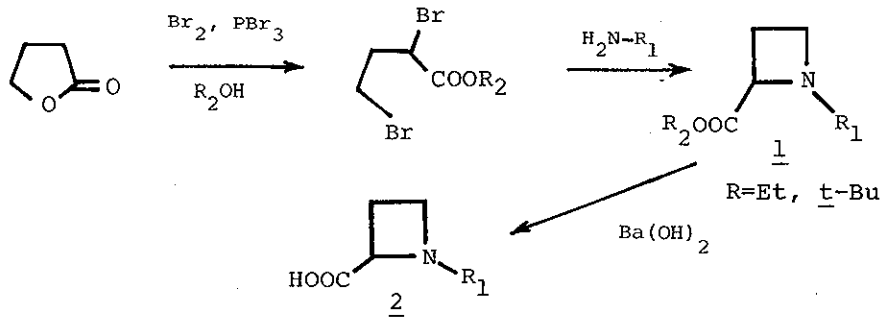
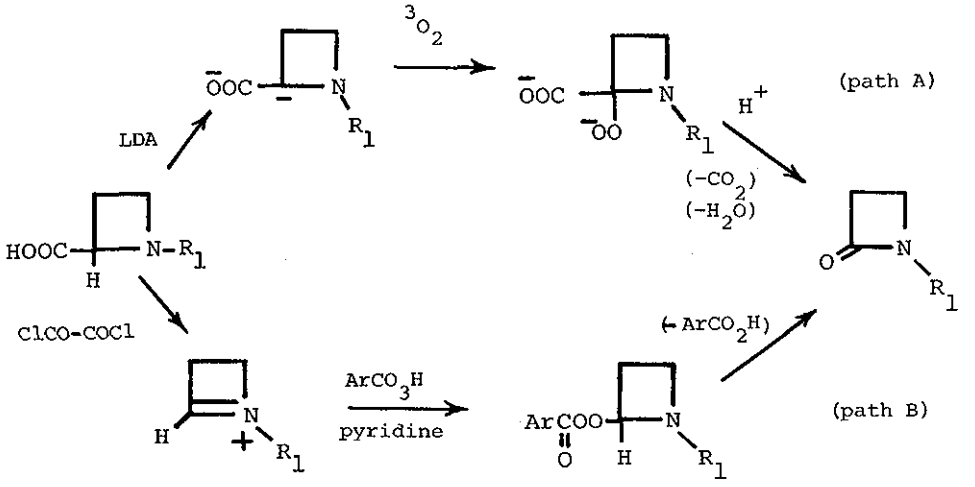
Azetidine carboxylic esters may be converted to enol silyl ethers which, as enamino ketene acetals, undergo ready oxidative cleavage of the carbon-carbon double bond by dye-sensitized photooxygenation to form β-lactams.

Azetidine carboxylic acids are readily available from γ-butyrolactone by the following bromination – substitution – hydrolysis sequence.[1]

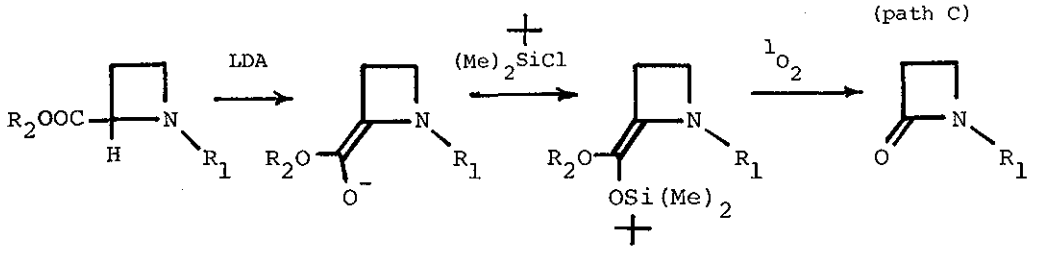


These azetidine derivatives are attractive precursors of β-lactams, and their utility in this conversion has been the subject

of two recent reports.[2,3] These earlier communications describe an oxidative decarboxylation process (path A), and a decarbonylation-peracid oxidation sequence (path B).



We now report a new method for the formation of β-lactams starting with the esters of azetidine carboxylic acids. In this procedure, the monoanion (3) of the ester (1) is formed by reaction with lithium diisopropylamide (LDA) in THF at -78°. The anion is treated with t-butyldimethylchlorosilane[4] and then subjected to dye-sensitized photooxygenation.[5] Oxidative cleavage of the intermediate enamino ketene acetal (4)[6] takes place rapidly under mild conditions to yield the β-lactam (5).



1 3 4 5

This procedure (path C) avoids the hydrolysis step (1→2) and has advantages over the earlier methods[2,3] in that it does not employ the strongly acidic conditions of oxalyl chloride and perchloric acid called for in path B.[3] Furthermore, β-lactam formation takes place in the presence of activated hydrogens located in the residue (R_1) attached to nitrogen. We have found[8] that such labile (benzylic or allylic) protons may compete favorably in the formation of dianions under the strongly basic conditions of path A.

Table I

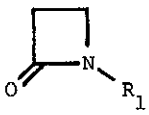
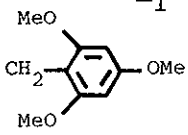
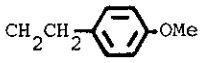
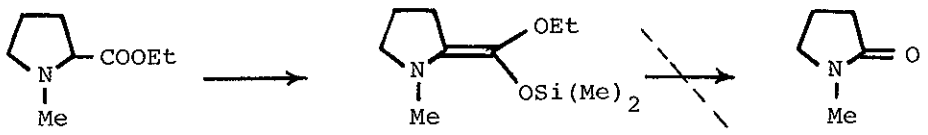
β-Lactam (5)		R_1	(yield, %)
	(a)		56
	(b)	$CH_2-CH=CH_2$	48
	(c)		66
	(d)		50
5a	(e)	$CH_2CH(OCH_3)_2$	56
	(f)	$CH(C_6H_5)_2$	55

Table I[10,11] shows some β-lactams prepared by this route. The method is illustrated in the preparation of N-(2,4,6-trimethoxybenzyl)-2-azetidinone (5a). To a solution of 1.2 mmol of LDA in 10 ml THF, cooled to -78° was added 337 mg (1 mmol) of azetidine

carboxylic ester (1, R_2=t-Bu, R_1=2,4,6-trimethoxybenzyl) in 3 ml THF. After stirring for 20 min, 200 mg (1.33 mmol) of t-butyldimethylchlorosilane in 2 ml THF was added. This solution was allowed to warm to room temperature over 1 hr, and then transferred to the well of an oxygenation apparatus[9] containing ca. 10 mg Rose Bengal in 50 ml of THF. After the solution was diluted with 50 ml of pentane, it was photooxygenated at 0-5° with internal irradiation (Sylvania DWY 650 watt source @ 100 volts). After 5 min, during which ca. 1 equiv of oxygen was consumed, the solution was poured into cold saturated ammonium chloride and extracted several times with ether. The combined extracts were washed with saturated sodium chloride solution and dried over magnesium sulfate. Concentration in vacuo followed by chromatography on silica gel ($CHCl_3$) yielded the lactam (5a) 140 mg (56%): ir (liquid film) cm^{-1} 1745, 1600; nmr ($CDCl_3$) δ 6.09 (2H, s), 4.36 (2H, s), 3.79 (6H, s), 3.75 (3H, s), 2.98 (2H, t, J=4 Hz), 2.74 (2H, t, J=4 Hz). Calcd for $C_{13}H_{17}NO_4$: 251.1156. Found: 251.1176.

When attempts were made to extend the silylation-oxidation sequence (path C) to the 5- and 6-membered ring analogs, N-methylproline ethyl ester (6)[12] and N-methylpipecolinic acid ethyl ester (7)[13], the reaction took a different course. Formation of the enol silylate followed by treatment with singlet oxygen as described above yielded none of the corresponding γ- or δ-lactams. Instead, low yields of the pyrrole (8) and the α,β-unsaturated ester (9) respectively were isolated. Further work is in progress to test the scope of this reaction.



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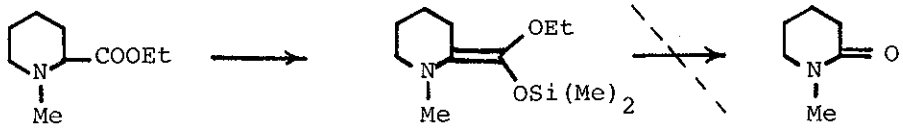

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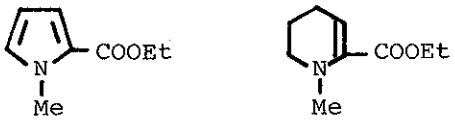

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References and Notes

1. N. H. Cromwell and R. M. Rodebaugh, J. Heterocyclic Chem., 1969, 6, 435.
2. H. H. Wasserman and B. H. Lipshutz, Tetrahedron Lett., 1976, 4613.
3. H. H. Wasserman and A. W. Tremper, Tetrahedron Lett., 1977, 1449.

4. Other silylating reagents, including trimethylsilyl chloride, n-butyldimethylsilyl chloride and s-butyldimethylsilyl chloride gave somewhat poorer yields of β-lactams.
5. Use of ozone for the oxidative cleavage of the ketene acetals (4) gave low yields (ca. 10%) of β-lactams, as well as products of further oxidation and decomposition.
6. Enamino ketene acetals of this type, to the best of our knowledge, have not been previously prepared.[7]
7. For a very recent review of O-silylated enolates, see J. K. Rasmussen, Synthesis, 1977, 91.
8. H. H. Wasserman and B. H. Lipshutz, unpublished results.
9. C. S. Foote and R. S. Vickers, Boll. Chim. Farm., 1970, 109, 599.
10. Satisfactory ir, nmr, and mass spectral data were obtained for all new compounds. The elemental analyses or high resolution mass spectra are consistent with the assigned structures.
11. The authors thank Dr. W. McMurray for running the high resolution mass spectra.
12. R. Willstaetter and F. Ettlinger, Ann., 1903, 326, 126.
13. K. Hess and F.Leibbrandt, Chem. Ber., 1917, 50, 385.

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