

SYNTHESIS AND INTRAMOLECULAR RING
CLEAVAGE OF 2-OXETANONES

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Summary: Intermolecular 2 + 2 aldehyde-ketene cycloaddition, followed by Lewis acid induced intramolecular ring opening of the 2-oxetanone product have been used to prepare tetrahydrofuran and tetrahydropyran ring systems.

Among lactones, 2-oxetanones are characterized by their readiness to undergo ring-opening reactions. Moreover, the variety of ways in which this can occur is the real mark of their versatility as synthetic intermediates.¹

The lability of the β C-O bond of 2-oxetanones, particularly in Lewis acidic environments, has been used to effect intermolecular C-C^{1c} and C-heteroatom^{1d} bond formation regioselectively (equation 1, figure 1). However, the intramolecular version of this reaction process (equation 2, figure 1) has remained largely unexploited.² In view of the high degree of control with which 4-substituted 2-oxetanones can be functionalized³, it appeared that a number of cyclic systems bearing α -chirality might be accessible by way of this methodology.⁴

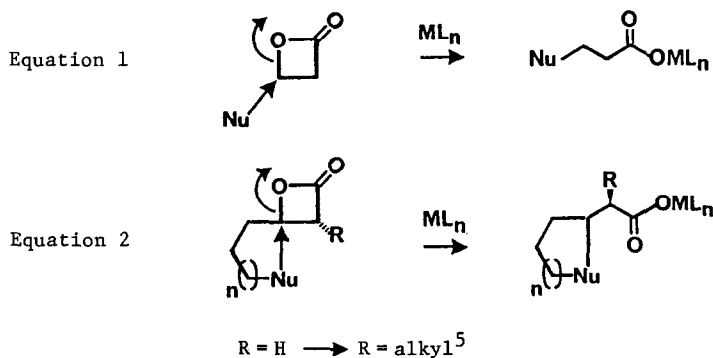


Figure 1

To test the feasibility of this approach we chose to prepare and study lactone 1, reasoning that under Lewis acid catalysis tetrahydrofuran ring formation from this would proceed rapidly and irreversibly to give benzylester 2, as outlined in figure 2.

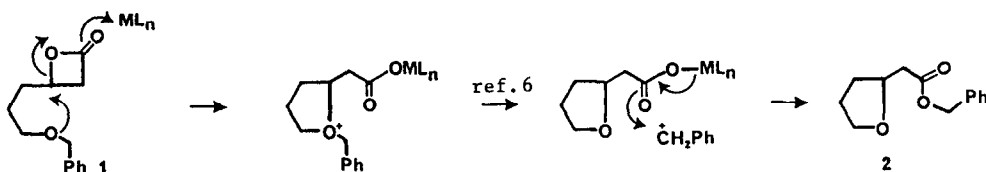


Figure 2

For the preparation of lactone 1, β -hydroxyacid 3 ($x=OH$, figure 3) seemed to be an obvious precursor.⁷ However, in our hands condensation of 4-benzyloxybutanal with the dianion of acetic acid⁸ gave an unacceptable yield (< 30%) of the desired product. Faced with this, we turned to a procedure first described by Masamune.⁹ Thus, reaction of the same aldehyde with the enolate of phenylthioacetate¹⁰ gave the thioester 3 ($x=SPh$) in 52% yield, which on exposure to mercuric mesylate in acetonitrile rapidly cyclized to lactone 1, along with a minor unidentified product which could not be removed by column chromatography. Nevertheless, treatment of this mixture with excess boron trifluoride etherate (CH_2Cl_2 , $0^\circ C$) led to a major product which, after chromatographic purification, was identified as the benzyl ester 2. Evidence in support of this assignment included the position of the benzyl protons in the 1H NMR spectrum, 0.63ppm downfield from those in the lactone 1, and the appearance of a strong band at 1750 cm^{-1} in the infrared spectrum.

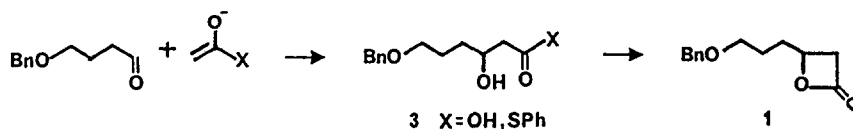


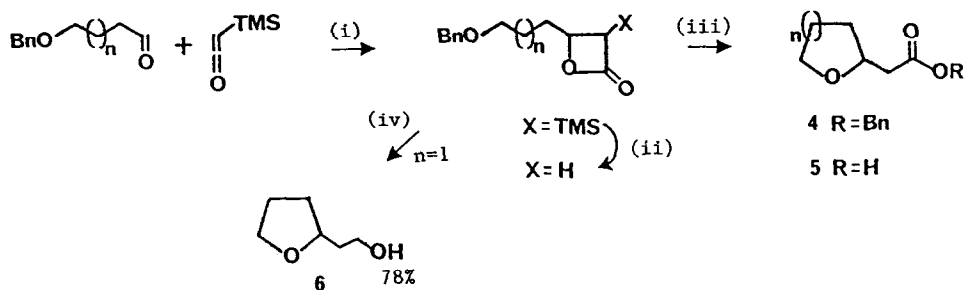
Figure 3

Having answered one question, an improved route to lactone 1 from 4-benzyloxybutanal became the next goal, at which point a 2 + 2 ketene-carbonyl cycloaddition reaction was considered. Although ketene itself is known to add efficiently to α -chloroaldehydes¹¹, reactions with unactivated carbonyls have generally proven less fruitful. Some years ago, Brady¹² showed that trimethylsilylketene - a thermally stable, distillable liquid¹³ - adds to aldehydes in good yield under boron trifluoride etherate catalysis. We were delighted to find that the TMS-lactone obtained using a modification of his procedure was stable to the conditions of its formation.¹⁴ Furthermore, the free lactone 1¹⁵ was cleanly generated when the crude product was stirred with potassium fluoride dihydrate in acetonitrile at room temperature (figure 4).

The success of the 2 + 2 cycloaddition was found to be critically dependent on the order in which the reagents were combined (see procedure). Slow addition of the ketene to a mixture of the aldehyde and Lewis acid, as described by Brady, gave product yields in the order of 50% for the two-step transformation.

In studying intramolecular ring openings, the effect of the size of the ring being formed became apparent. Whereas tetrahydrofuran ring formation occurred within thirty minutes at $-20^\circ C$, an ice-bath temperature for several hours was required to take tetrahydropyran ring formation to its completion (see figure 4 and table of results). On further examination, the free acids 5 were found to be minor products of reaction. For this reason, reduction of the mixture of 4 and 5 to the alcohol 6 before purification provided a more accurate

measure of the overall efficiency of intramolecular ring opening.



(i) Cat. $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 0°C ; (ii) $\text{KF} \cdot 2\text{H}_2\text{O}$, CH_3CN ; (iii) $2\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 ; ¹⁶
 (iv) (a) (iii) (b) LiAlH_4 , Et_2O

Figure 4

Table of Results

	% Yield of 2-oxetanone (x = H)	Oxetanone Ring Opening	
		Temperature ($^\circ\text{C}$)	Yield of 4 (%)
n = 1	81	-20	69
n = 2	71	0	65

Preparation of Lactone 1

A solution of 4-benzyloxybutanal (0.5g, 2.8mmol) and trimethylsilylketene (0.35g, 3.1 mmol) in methylene chloride (5ml) was cooled to 0°C . With stirring, boron trifluoride etherate (approximately 0.4ml of a 0.1M solution in CH_2Cl_2)¹⁷ was added dropwise until TLC indicated complete loss of starting material. Two drops of water were added and the organic solution was transferred by pipette onto anhydrous sodium sulfate, and then into a clean reaction flask where it was concentrated to an oil under reduced pressure. Acetonitrile (7ml) was added followed by finely crushed potassium fluoride dihydrate (0.5g, 5.3mmol) and the mixture stirred vigorously for 20 minutes at room temperature. The resulting mixture was filtered through fluorisil with ether washing and concentrated to an almost colorless oil. Silica gel chromatography (20:1 petroleum ether - ether) gave 503 mg of lactone **1** (81%).

Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References and Notes

1. For selected examples, see: (a) T. H. Black, J. A. Hall, and R. G. Sheu, *J. Org. Chem.*, 1988, 53, 2371 and references cited therein; (b) W. T. Brady, Y-S. F. Giang, A. P. Marchand, and A-h. Wu, *ibid.*, 1987, 52, 3457; (c) L. D. Arnold, J. C. G. Drover, and J. C. Vederas, *J. Am. Chem. Soc.*, 1987, 109, 4649 and references cited therein; (d) L. D. Arnold, T. H. Kalantar, and J. C. Vederas, *J. Am. Chem. Soc.*, 1985, 107, 7105; (d) T. Izawa and T. Mukaiyama, *Chem. Lett.*, 1978, 409.
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14. Although the silyl-substituted 2-oxetanone was not isolated, an IR spectrum of the crude oil following cycloaddition showed a strong carbonyl stretch at 1810cm⁻¹.
15. IR 1845cm⁻¹ (C = O); 60 MHz NMR (CDCl₃) δ1.50 - 2.10 (4H, m), 2.80 - 3.70 (4H, m), 4.50 (3H, bs), 7.93 (5H, bs).
16. The addition of just one equivalent of the Lewis acid resulted in longer reaction times.
17. Product yields for this reaction were found to be significantly lower when higher concentrations of the Lewis acid were employed.

(Received in USA 23 September 1988)