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One-Carbon Ring Enlargement of Lactones

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Abstract: Two-step or three-step one-carbon ring enlargement of lactones is realized from lactones and chloromethyl phenyl sulfoxide via a rearrangement of alkylidene carbenoid followed by intramolecular cyclization of the ω -hydroxyalkyl ketene intermediate or via a 2-pyridinethiol ester. © 1998 Elsevier Science Ltd. All rights reserved.

Ring enlargement is a quite interesting and important method for obtaining the desired cyclic compounds from lower cyclic compounds.¹ There are many one-carbon ring enlargement reactions for carbocyclic compounds and cyclic ketones; however, the one-carbon ring enlargement of lactones is rare.²

Recently, we reported a new method for synthesis of carboxylic acids and their derivatives from methyl esters with one-carbon homologation.³ In this letter, in continuation of our studies on the homologation of carbonyl compounds,⁴ we describe a novel two-step or three-step procedure for one-carbon enlargement of lactones 1 via carbenoid rearrangement (to give alkynolate 4) and ω -hydroxy ketenes 5 or via 2-pyridinethiol esters 6⁵ (Scheme 1).



The described procedure uses γ -phenyl γ -butyrolactone 7 as a typical lactone (Scheme 2). Reaction of the lithium carbanion of chloromethyl phenyl sulfoxide with 7 at -78 °C afforded a diastereomeric mixture of the adduct 8 in 94% yield.³ The structure of the adduct was found not to be the α -sulfinyl ketone but a hemiacetal. The adduct 8 was treated with three equivalents of KH in THF at 0 °C for 30 min, then the reaction mixture was cooled to -78 °C. To the solution of the potassium enolate, four equivalents of *t*-BuLi were added and the reaction mixture was stirred at -78 °C for 20 min. Finally, in order to generate the ω -hydroxyalkyl ketene, the

reaction was quenched by adding a proton source. We expected that if the above-mentioned treatment gave the ω -hydroxyalkyl ketene, it would be cyclized to give δ -phenyl δ -valerolactone 9.⁶

Scheme 2 Ph $- \begin{pmatrix} - \\ 0 \end{pmatrix}$ 7	$O = \frac{\frac{PhSCH_2Cl}{PhSCH_2Cl}}{THF, -78 °C}$	$\xrightarrow{DA} Ph - OH - OH - S(O) - S(O) - S(O)$	Ph 1) KH Ph 2) t-BuLi 3) proton source	
-	Proton source	Conditions	Concentration mol / L	9 (Yield/%)
_	Et ₃ N HCl (8 eq.)	-78 °C 1 h, then 0 °C 1 h	0.1	45
	Et ₃ N HCl (Finely ground; 8 eq.)	-78 °C 1 h, then 0 °C 2 h	0.1	59
	H ₂ SO ₄ (3 eq.)	-78 °C 1 h, then 0 °C 1 h	0.05	69

First, the above-mentioned reaction was treated with 8 equivalents of dry triethylamine hydrochloride.⁷ Fortunately, this treatment gave the desired one-carbon homologated lactone 9 in 45% yield. The yield was improved to 59% by using finely ground, dry triethylamine hydrochloride. After some investigation, the best yield (69%) was obtained with 95% sulfuric acid⁸ (Scheme 2).

The preliminary results for the one-carbon ring enlargement of 5-, 6-, and 9-membered lactones are summarized in Table 1. Entries 1-5 show that the reaction of the lithium carbanion of chloromethyl phenyl sulfoxide with γ - and δ -lactones gave a diastereometric mixture of hemiacetals in almost quantitative yields. In the case of the 9-membered lactone, the adduct was found to be β -ketosulfoxide (entry 6).

Formation of a potassium enolate of the adducts and the treatment of the generated enolate with *t*-BuLi followed by sulfuric acid was carried out in a similar way to that described above. Entries 1-3 indicate that the reaction proceeded smoothly to give the desired one-carbon homologated δ -lactones in good yields. In contrast to this, conversion of the 6-membered lactones to 7-membered lactones (entries 4 and 5) was found to be problematical. Especially the reaction shown in entry 5 gave only a complex mixture when the reaction was carried out at the concentration of 0.05 mol/L. Even in a much more diluted solution, the yield of the desired lactone was low. The by-products of this reaction were thought to be dimer, trimer, and polymers, although they have not be isolated yet.

Entry 6 shows that the reaction of β -ketosulfoxide to 10-membered lactone (medium-sized cyclic compound) also is very difficult.

Synthesis of macro lactones is an interesting subject. We tried to synthesize macrolides by using our abovementioned method (Scheme 3). 13-Membered lactone was reacted with chloromethyl phenyl sulfoxide to give the desired β -ketosulfoxide 10 in 94% yield. This sulfoxide was treated with KH-*t*-BuLi, followed by sulfuric acid. However, the treatment again gave only a complex mixture. We then changed to use of the so-called Mukaiyama-Corey method.^{5, 9)}

Lactor	PhSCH ₂ CI ae	$ \begin{array}{c} R \leftarrow ()_n \\ O \qquad OH \\ O \qquad S(O)Ph \\ 3 CI \end{array} $	1) KH 2) <i>t</i> -BuLi 3) H ₂ SO ₄	
Entry	Lactone	3 (Yield / %) ^{a)}	Conc. (mol/L) ^b	$\frac{2}{(\text{Yield } / \%)^{c)}}$
I	Ph-CoCo	(94)	0.05	Ph-0-0 (69)
2	т-C ₆ H ₁₃ (0)0	(94)	0.05	<i>n</i> -C ₆ H ₁₃ (59)
3		'h (88)	0.05	Ph O (65)
4		(91)	0.0 5	
5	<i>n</i> -C ₇ H ₁₅ −↓0	(91)	0.005 ^{d)}	<i>n</i> -C ₇ H ₁₅
6	A	CI SPh	0.05	complex mixture
	[、] o本o	ОН (94	0.005	complex mixture

Table 1. One-Carbon Ring Enlargement of 5-, 6-, and 9-Membered Lactones





We have already reported one-carbon homologation of methylesters to thiol esters.³⁾ β -Ketosulfoxide 10 was treated with KH-*t*-BuLi as above and the reaction was finally treated with 2-mercaptopyridine. Fortunately, this reaction gave the desired 2-pyridinethiol ester 11 in 60% yield. Corey and Nicolaou have already converted 11 to 14-membered lactone 12 in 68% yield.^{5a)}

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- 7. Commercial triethylamine hydrochloride was dried over P_2O_5 under vacuum.
- 8. In a 30-ml flame-dried flask was added KH (36 mg; 0.9 mmol) and 3 ml of dry THF. This suspension was cooled in an ice bath and to this was added a solution of 8 (101 mg; 0.3 mmol) in 1 ml of dry THF. The reaction mixture was stirred at 0 °C for 30 min. Within this time the evolution of H₂ ceased. The reaction mixture was cooled to -78 °C. *t*-BuLi (1.6M in pentane; 0.73 ml; 1.2 mmol) was added dropwise to the reaction mixture and the solution was stirred at -78 °C for 20 min. A solution of 95% sulfuric acid (0.05l ml; 0.9 mmol) in 2 ml of THF was added dropwise to the reaction mixture and the solution was stirred at -78 °C for 20 min. A solution of 95% sulfuric acid (0.05l ml; 0.9 mmol) in 2 ml of THF was added dropwise to the reaction mixture and the solution was stirred at -78 °C for 1 h and at 0 °C for 1 h. The reaction was quenched by adding sat. aq NH₄Cl and the whole was extracted with benzene-ether. The organic layer was washed once with sat. aq. NH₄Cl and dried over MgSO₄. The product was purified by silica gel column chromatography (Hexane:AcOEt=5:1) to give 9 (36.6 mg; 69%) as a colorless oil.
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