

REACTION OF ENOLATE ANIONS WITH LACTONES

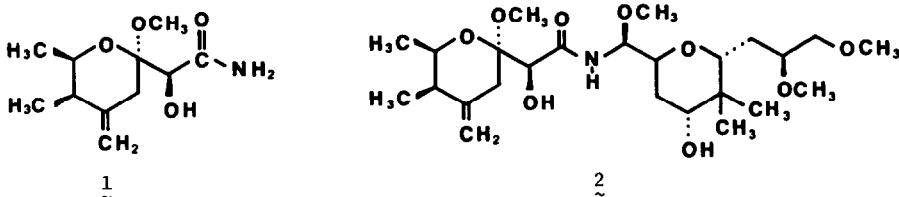
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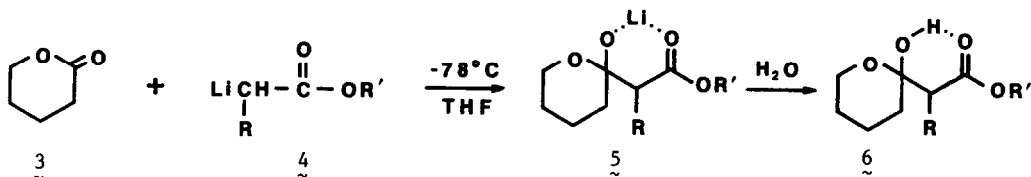
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In the course of our studies directed towards the synthesis of pederamide (1)¹⁻³, a degradation product of pederin (2)⁴, we had occasion to explore the chemistry of carbanion additions to the carbonyl group of lactones. Herein, we describe the results of our studies in which δ -valerolactone and γ -butyrolactone were treated with enolate anions which contained the latent functionality of the glycolamide side chain of pederamide.



Although the reaction of lactones with two equivalents of alkyl anion donors, such as Grignard reagents and alkylolithiums, is an excellent method of preparing diols⁵, the addition at low temperature of one equivalent of the nucleophile can be controlled to yield keto-alcohols in reasonable yield⁶. Similarly, we have observed that stabilized anions, such as ester enolates and enolates of phosphonitriles, condense with lactones in good yield to form products derived from a single addition.



Lithium ester enolates react with δ -valerolactone to yield products which exist as cyclic hemiketals without significant amounts of the ring opened ketol (Table I).⁷ The preference for the cyclic hemiketal over the open keto form may be due to the stabilization of the hemiketal via lithium chelation (5) and subsequent hydrogen bonding with the ester carbonyl (6a-6g).

TABLE I
Reaction of Lithium Ester Enolates with Lactones^a

Lithium Enolate	R	R'	Yield (%) δ -Valerolactone	Yield (%) γ -Butyrolactone
4a	H	\underline{t} -C ₄ H ₉	6a 97 (73) ^b	7a 95 ^{d,g}
4b	H	C ₂ H ₅	6b 60 (50) ^b	
4c	\underline{O} -C ₄ H ₉	\underline{t} -C ₄ H ₉	6c 87 ^{c,d}	
4d	$\begin{array}{c} \text{H} \\ \\ \text{O}-\text{C}-\text{OC}_2\text{H}_5 \\ \\ \text{CH}_3 \end{array}$	CH ₃	6d 85 ^{d,e}	
4e	\underline{O} -C ₄ H ₉	C ₂ H ₅	6e 85 ^{d,f}	
4f	$\begin{array}{c} \text{CH}_3 \\ \\ \text{O}-\text{C}-\text{OCH}_3 \\ \\ \text{CH}_3 \end{array}$	C ₂ H ₅	6f 71 ^{d,g}	7b 50 ^h
4g	O-CH ₂ -C ₆ H ₅	C ₂ H ₅	6g 66 ^h	
4h	Br	\underline{t} -C ₄ H ₉	N.R.	

^aEach product had IR, NMR, and MS data in accord with the assigned structure.

^bPurified by Kugelrohr distillation at reduced pressure.

^cMixture of stereoisomers, mp 71-74°C.

^dCrude, yield not optimized.

^eContained self-condensation products of the ester enolate.

^fContained starting ester from enolate exchange.

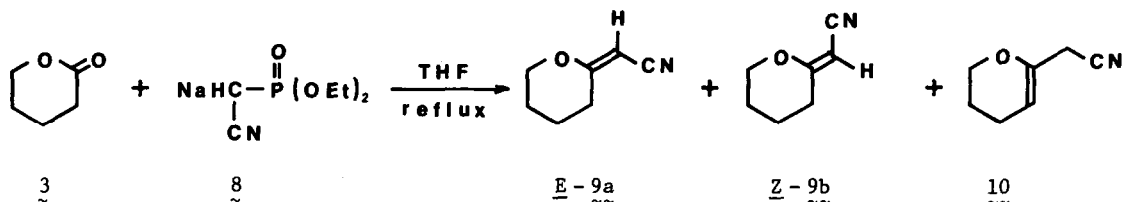
^gOne TLC spot; no evidence (NMR) of self-condensation products or starting ester.

^hPurified by medium pressure LC on silica gel.

The reaction proceeds most effectively with \underline{t} -butyl esters. The less hindered esters were prone to give side-products derived from self-condensation of the ester enolates and incomplete reaction due to quenching of the anion by proton abstraction from the δ -valerolactone. Although the glycolic esters condense satisfactorily, α -halo esters (which would give the analog of the Darzens reaction)⁸ do not react. The reaction of δ -valerolactone with dianions derived from either glycolic acids or glycolamides was also unsuccessful.⁹ A study with γ -butyrolactone (Table I) revealed that the reaction of γ -lactones proceeds analogously, forming the corresponding hemiketals 7a and 7b in good yield.

Attempts to condense the sodium ester enolate of triethylphosphonoacetate (Wadsworth-Emmons reaction)¹⁰ with δ -valerolactone were not successful. Although an exothermic reaction was observed upon the addition of the lactone to the enolate, work-up afforded the starting reagents. This suggests that enolate exchange rather than betaine formation occurred. A similar exothermic reaction was observed when δ -valerolactone and the sodium enolate of diethylcyanomethylphosphonate (8) were mixed, but refluxing the THF solution resulted in the formation of sodium diethylphosphate. Work-up afforded a 75% yield of a 1:1 mixture of the E and Z isomers¹¹ of the exocyclic olefin 9,

along with varying amounts of the endocyclic isomer 10. The isomers are readily separated by careful column chromatography on alumina.



The analogous reaction with γ -butyrolactone gave a 52% yield of products which comprised a mixture of 27% E isomer, 17% Z isomer and 8% of a third product, 3-tetrahydrofuran-2-ylidene butyrolactone, resulting from the self-condensation of γ -butyrolactone. The endocyclic double bond isomer was not detected.

EXPERIMENTAL

I. Ethyl-2-hydroxy-tetrahydro-2H-pyran-2-[α -(2-methoxyprop-2-yl)oxy]acetate (6f): A solution of diisopropylamide, which was generated at 0°C from diisopropylamine (1.21 g, 0.012 mol/5 mL of THF) and n-butyllithium (0.01 mol of a 2.2 M solution in hexane) was cooled to -75°C. The glycolic ester 4f (2.15 g, 0.012 mol/5 mL THF) was added dropwise, maintained at -75°C for 45 min, and the δ -valerolactone (1.0 g, 0.01 mol/4 mL of THF) was added to the ester enolate. The reaction mixture was kept at -75°C for 2 h, quenched with 2 mL of EtOH and warmed to ambient temperature. The products were partitioned between Et₂O and water, and the ether layer was dried over K₂CO₃, and concentrated to afford 1.96 g (71%) of the hemiketal 6f which appeared homogeneous by TLC. 6f: NMR (CDCl₃) δ 1.11 (3 H, t, J = 6 Hz), 1.35 (8 H, m), 1.74 (4 H, m), 3.23 (3 H, s), 3.24 (3 H, m), 4.05 (1 H, s), 4.25 (2 H, q, J = 6 Hz); CIMS m/e (rel intensity) 187 (6, M⁺ - C(CH₃)₂OCH₃), 73 (100).

II. Tetrahydropyran-2-ylidenecyanomethane (9): The sodium enolate was generated at 5°C from NaH (2.13 g, 0.051 mol of a 57% oil dispersion which had been washed with pentane to remove the oil) in 20 mL of THF and diethylcyanomethylphosphonate (8.5 g, 0.05 mol/20 mL of THF). The reaction mixture was warmed to 20°C and δ -valerolactone (5.0 g, 0.05 mol) was added < 30°C. The reaction mixture was refluxed 2 h, cooled to 25°C and the gummy sodium diethylphosphate was dissolved in water. The aqueous layer was saturated with NaCl, extracted with Et₂O and the Et₂O was dried over MgSO₄, filtered and concentrated to yield a yellow oil which was dissolved in hexane. Filtration through alumina (Grade I) afforded 4.6 g (75%) of a colorless oil which was a mixture of the exocyclic (9) and endocyclic (10) isomers. The isomers were separated on alumina (Grade I), eluting with ether-benzene mixtures. E-9a: IR (CHCl₃) 1628 cm⁻¹; NMR (CDCl₃) δ 1.80 (4 H, m), 2.62 (2 H, m), 4.05 (2 H, m), 4.58 (1 H, s); CIMS m/e (rel intensity) 124 (100, M⁺ + 1), 75 (11). Z-9b: IR (CHCl₃) 1630 cm⁻¹; NMR (CDCl₃) δ 1.84 (4 H, m), 2.35 (2 H, m), 4.14 (2 H, m), 4.27 (1 H, m); CIMS m/e (rel intensity) 124 (100, M⁺ + 1), 75 (11). Endocyclic 10: IR (CHCl₃) 1674 cm⁻¹; NMR (CDCl₃) δ 1.77 (2 H, m), 2.02 (2 H, m), 3.03 (2 H, m), 4.0 (2 H, m), 4.82 (1 H, m); CIMS m/e (rel intensity) 124 (100, M⁺ + 1).

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12. In the presence of THF-N(Et)₃, pure 9a or 9b equilibrate to a mixture of E and Z isomers and 10.

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