

Reactions of β -Lactones with Potassium Alkoxides and Their Complexes with 18-Crown-6 in Aprotic Solvents

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The mechanism of the reaction of β -lactones (2-oxetanones) with potassium alkoxides in aprotic solvents was investigated. Despite previous suggestions, the attack of alkoxide ion occurs on the carbonyl carbon atom of β -lactones, cleaving the acyl-oxygen bond to yield the corresponding potassium alcoholate of the respective β -hydroxycarboxylic acid ester. Next, the unsaturated ester is formed due to potassium hydroxide elimination. The nature of the alkoxide used and complexation of alkali metal cation by crown ether have no significant effect on the reaction course in aprotic solvents.

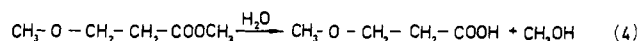
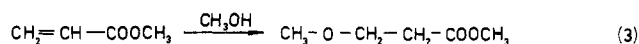
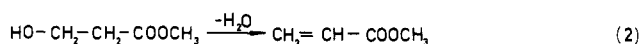
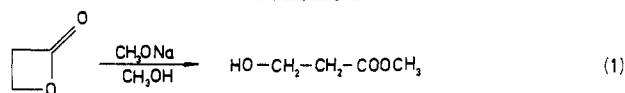
The chemistry of β -lactones (2-oxetanones) has been of ongoing interest because of their utility in the preparation of biologically active materials. Besides numerous published syntheses of biodegradable polymers through the polymerization of β -methyl- β -propiolactone (β -butyrolactone),¹ the base alcoholysis of α,α -diphenyl- β -propiolactone has also been studied in hopes of preparing the corresponding analogues of tropic acid esters, which exhibit a high order of antispasmodic activity.²

According to Gresham *et al.*,³ the base-catalyzed reaction of β -propiolactone with sodium methoxide and an excess of methanol gives methyl β -hydroxypropionate. However, some years later, Bartlett and Rylander demonstrated that methyl β -methoxypropionate (or, after hydrolysis, β -methoxypropionic acid) was the final product of the reaction between β -propiolactone and sodium methoxide.⁴ The reaction proceeds through several steps: (1) First, methanolysis and ring cleavage of the β -propiolactone takes place due to acyl-oxygen bond scission. (2) In the second step, base-catalyzed dehydration yields methyl acrylate. (3) Addition of methanol to the double bond yields methyl β -methoxypropionate. (4) Eventually, hydrolysis of the latter by the water produced in the previous step (2) may yield β -methoxypropionic acid (Scheme I).

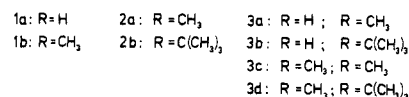
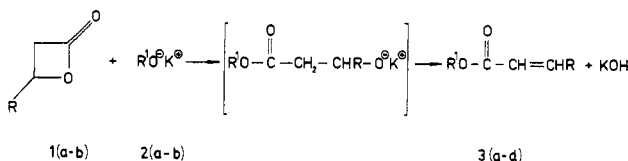
It was claimed recently that, in the reaction of β -propiolactone and potassium methoxide in DMF (i.e. in aprotic solvent), the potassium salt of β -methoxypropionic acid and the potassium alcoholate of β -hydroxypropionic acid methyl ester are formed due to both acyl-oxygen and alkyl-oxygen bond cleavage.⁵ This mechanism is inconsistent with later suggestions that in THF solution, potassium *tert*-butoxide deprotonates β -lactones (β -propiolactone and β -butyrolactone), and the corresponding salts of α,β -unsaturated carboxylic acids are formed.^{6,7}

The discrepancies in the literature prompted us to reinvestigate the reaction of simple β -lactones: β -propiolactone 1a and β -methyl- β -propiolactone (1b) (β -butyrolactone), with potassium methoxide (2a) and potassium *tert*-butoxide (2b), in THF and DMF. The experimental

Scheme I



Scheme II



results indicate that the attack of alkoxide ion occurs on the carbonyl carbon atom of β -lactones, cleaving the acyl-oxygen bond, to yield the corresponding potassium alcoholate of the respective β -hydroxycarboxylic acid ester. Next, unsaturated ester 3 is formed, due to potassium hydroxide elimination (Scheme II). The corresponding esters of acrylic acids 3a,b or crotonic acids 3c,d have been isolated, as described in the Experimental Section, with yields of about 90% (Table I). The addition of 18-crown-6 and the complexation of potassium cation have no significant influence on the reaction course in the solvents used. The reaction course has also been followed by ¹H NMR (300 MHz). The experiment was conducted in the NMR spectrometer tube in THF-*d*₈. After completion of the reaction between potassium *tert*-butoxide (2b) and lactone 1b (15 min), the signals corresponding to the protons of 1b and 2b disappeared and those of ester 3d (*tert*-butyl crotonate)⁸ were observed. In a control experiment, 3-hydroxybutyric acid ester reacted with NaH to yield the corresponding unsaturated ester.⁹

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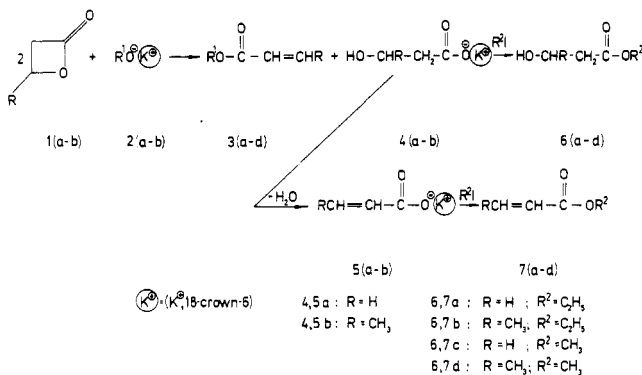
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Table I. Products of Equimolar Reaction of Lactones 1 with Potassium Alkoxides 2 in THF at 20 °C

lactone	alkoxide	product	R	R ¹	yield, ^a %
1a	2a	3a	H	CH ₃	90
1a	2b	3b	H	C(CH ₃) ₃	96
1b	2a	3c ^b	CH ₃	CH ₃	87
1b	2b	3d ^c	CH ₃	C(CH ₃) ₃	97

^a Yield of isolated products based on reaction lactones. ^b Mole ratio of isomer *Z* to *E* 1:15. ^c Mole ratio of isomer *Z* to *E* 1:45.

Scheme III**Table II. Products of 2:1 Mole Ratio Reaction of β -Lactones 1 with 18-Crown-6 Complexes of Potassium Alkoxides 2 in THF at 20 °C**

lactone	alkoxide	alkylating agent	products (yield, ^a %)		
			3	6	7
1a	2a/18C6	C ₂ H ₅ I	3a (52)	6a (22)	7a (26)
1b	2a/18C6	C ₂ H ₅ I	3c ^b (51)	6b (18)	7b ^b (31)
1a	2b/18C6	CH ₃ I	3b (50)	6c (24)	7c (26)
1b	2b/18C6	CH ₃ I	3d ^b (54)	6d (20)	7d ^b (26)

^a Yields are reported as uncorrected GC areas. ^b Total yield of *Z* and *E* isomers.

In the cases involving β -lactone in excess (molar ratio of lactone to alkoxide 2:1), the potassium hydroxide formed (Scheme II) reacted with another molecule of β -lactone by attacking the carbonyl carbon atom, yielding potassium salts of the corresponding β -hydroxy acids 4, and salts of the corresponding unsaturated acids 5, formed due to the partial dehydration of 4. Alkylation of salts 4 and 5 led to the corresponding esters 6 and 7, in the presence of a crown ether,¹⁰ (Scheme III, Table II).

The experiments performed indicate that in the reaction of β -lactones with alkali metal alkoxides in aprotic solvents, contrary to previous suggestions, the corresponding unsaturated esters are formed in high yield due to β -lactone acyl-oxygen bond cleavage, accompanied by potassium hydroxide elimination. The nature of the alkoxide used, solvent (THF, DMF), and addition of a crown ether have no significant effect on the reaction course. These results clear up the controversy on the reactions between β -lactones with alkali metal alkoxides in aprotic solvents.

Experimental Section

The ¹H NMR spectra were recorded using a Varian VXR-300 spectrometer in CDCl₃ with TMS as internal standard. GC-MS analyses were run on 30-m long fused silica capillary column

(8) ¹H NMR (CDCl₃) δ 1.49 (s, 9H, (CH₃)₃COC(O)), 1.89 (d, 3H, CH₃-CH), 5.9 (d, 1H, CH), 6.9–7.1 (m, 1H, CHCH₂).

(9) In the reaction of 3-hydroxybutyric acid methyl ester with NaH the methyl crotonate 3c was formed (yield 90%): ¹H NMR (CDCl₃) δ 1.89 (d, 3H, CH₃CH), 3.73 (s, 3H, CH₃O), 5.9 (d, 1H, CH), 6.9–7.1 (m, 1H, CHCH₂).

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DB-1701, using a Varian 3300 gas chromatograph equipped with a Finnigan MAT 800AT ion trap detector. Preparative GC separations were conducted on a glass column packed with OV-17, 15% on Chromosorb W, 45–60 mesh using a Varian 2800 gas chromatograph with a semipreparative unit.

Materials. β -Propiolactone (1a) (from Aldrich) was dried as described previously.¹¹ The fraction boiling at 51 °C (10 mmHg) was collected. β -Butyrolactone (1b) (from Fluka) bp 47 °C (5 mmHg) was purified in a similar manner. 18-Crown-6 (from Fluka) was purified as described in ref 11. Potassium methoxide was obtained by reacting dry methanol with a potassium mirror. Its complex with 18-crown-6 (mole ratio 1:1) was obtained by adding an equimolar amount of the complexant to potassium methoxide solution in dry methanol. The excess methanol was then removed by evaporation. Potassium *tert*-butoxide/18-crown-6 complex (mole ratio 1:1) was obtained by dissolution of equimolar amounts of potassium *tert*-butoxide (from Aldrich) and crown ether in dry THF. THF was purified as described in ref 12 and was then distilled over a sodium-potassium alloy in an argon atmosphere. DMF was purified as described in ref 5. The ion-exchange resin, Lewatit S 1080 (from Merck) in acid form, was used as protonation agent. Methyl iodide and ethyl iodide (both from Aldrich) were used as alkylation agents.

General Procedure. Reaction of β -Lactones 1 with Alkali Metal Alkoxides 2 (Scheme II). Into the reaction vessel containing 0.02 mol of potassium alkoxide 2 in 20 mL of THF was added a solution consisting of an equimolar amount of 1 in 5 mL of THF dropwise under an argon atmosphere, at 20 °C with intensive stirring using a glass-covered magnetic stirring bar. After 15 min, 1.5 g of acidic ion-exchange resin (Lewatit S 1080) was introduced into the reaction mixture. After filtration, the final product was isolated from the THF solution by distillation under reduced pressure using a Hickman apparatus. Yields of isolated esters 3 are reported in Table I. The MS and NMR spectra of the obtained esters 3 were consistent with those of the original samples of authentic compounds.

Similar results were obtained for the reaction of lactones 1 in DMF and with the potassium alkoxide/18-crown-6 complexes.

The 2:1 Mole Ratio Reaction of β -Lactones 1 with 18-Crown-6 Complexes of Potassium Alkoxides 2 (Scheme III). The reactions in which the mole ratio of β -lactones 1 to 18-crown-6 complex of alkali metal alkoxides 2 was 2:1 were conducted similarly to those described above but instead of the ion-exchange resin, ethyl iodide (in reaction of 1 with 2a/18-crown-6 complex) and methyl iodide (in reaction of 1 with 2b/18-crown-6 complex) were added. The reaction mixture was filtered and the filtrate was analyzed by GC-MS technique. The composition of the products identified by GC-MS analysis are reported in Table II. The products were characterized on the basis of comparison of the retention times and mass spectra with those of the original samples or by computer comparison of the MS spectrum with the NBS mass spectra library. The β -hydroxy esters 6 have been separated by preparative GC and additionally characterized by ¹H NMR. 3-Hydroxypropanoic acid ethyl ester 6a: ¹H NMR (CDCl₃) δ 1.20 (t, 3H, CH₂CH₃), 2.46 (s, 1H, CH₂CH₂OH), 2.66 (t, 2H, CH₂CH₂OH), 3.95 (t, 2H, CH₂CH₂OH), 4.21 (q, 2H, OCH₂-CH₃) ppm. 3-Hydroxybutanoic acid ethyl ester 6b: ¹H NMR (CDCl₃) δ 1.20–1.34 (m, 6H, CH₂CH, CH₂CH₂), 2.34–2.54 (m, 3H, CH₂ and OH), 4.14–4.30 (m, 3H, CHOH, OCH₂CH₃) ppm. 3-Hydroxypropanoic acid methyl ester 6c: ¹H NMR (CDCl₃) δ 2.46 (s, 1H, CH₂CH₂OH), 2.66 (t, 2H, CH₂C(O)), 3.67 (s, 3H, CH₃O), 3.95 (t, 2H, OCH₂CH₂) ppm. 3-Hydroxybutanoic acid methyl ester 6d: ¹H NMR (CDCl₃) δ 1.23 (d, 3H, CH₃CH), 2.37–2.54 (m, 3H, CH₂ and OH), 3.69 (s, 3H, CH₃OC(O)), 4.14–4.23 (m, 1H, CHOH) ppm.

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