Tetrahedron Letters Vol. 21, pp 2181 - 2184
0040-4039/80/0522-2181$02.00/0

A THREE CARBON HOMOLOGATION BY THE RING-OPENING OF β-PROPIOLACTONES WITH DIORGANOCUPRATES

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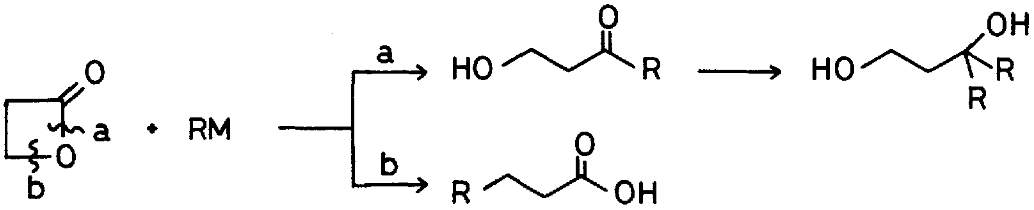
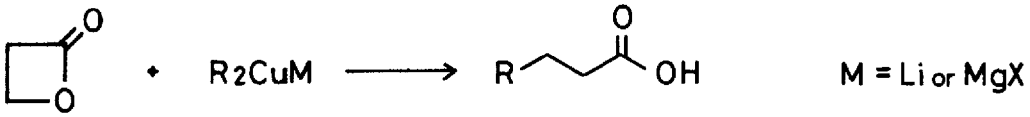
Summary; *Various organocuprates react with β-propiolactones to give β-substituted propionic acids in high yields.*

The nucleophilic ring opening of lactones by organometallic compounds is one of the useful methods for a carbon-carbon bond formation. There have been a number of reports on such a type of the reaction of five- and six-membered lactones.[1] However, a limited number of papers on the ring opening of four memberd lactones, β-propiolactones, by organometallic compounds[3,4] were reported so far, although the ring opening of the lactones by the hetero atoms such as halide ions, thiol, alcohol, amine and so on, to give β-substituted propionic acids is well documented.[2] A previous study by Stuckwisch et al.[4] has shown that the reaction of β-propiolactone with organometallic compounds such as Grignard reagents, organolithium and organocadmium compounds affords several types of products because of the duality of ring opening of β-propiolactone; i. e. (a) the carbonyl carbon-oxygen bond cleavage and (b) the methylene-oxygen bond cleavage. The latter type of the reaction provides a method of three carbon homologation terminated with a carboxyl group. The product of the reaction is equivalent to that of the conjugate addition to acrylic acid, which has never been achieved by using any organometallic reagent.[5] We wish to report here that



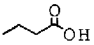
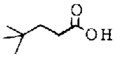
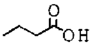
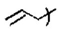
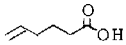
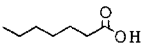
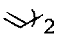
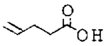
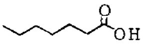
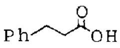
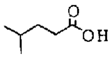
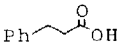
the regiospecific ring opening of β-propiolactones can be achieved by the use of organocuprates.

When lithium di-n-butylcuprate reacted with β-propiolactone in THF at -30°C, heptanoic acid was obtained in a yield of 83%. Although the cuprate was prepared from 2 equivalents of n-butyllithium and one equivalent of copper(I) iodide, bromomagnesium di-n-butylcuprate, which was prepared from 2 equivalents of n-butyl Grignard reagent and one equivalent of copper(I) iodide, gave the same product in higher yield by the reaction with β-propiolactone. There was some difference in the solubility between the both cuprates. Lithium di-n-butylcuprate dissolved both in ether and in THF, but bromomagnesium di-n-butylcuprate dissolved in neither of them. Accordingly, when homogeneous reaction using bromomagnesium di-n-butylcuprate was conducted by the addition of dimethyl sulfide as a co-solvent of THF, the yield of the product was increased.



The reaction of various types of organocuprates with β-propiolactone was studied as shown in the Table I. In the case of lithium cuprates, the reactivity was changed remarkably; e. g. lithium diphenylcuprate gave phenylprpionic acid in a yield of only 20%. Halomagnesium cuprates, however, attacked regiospecifically to the methylene carbon of β-propiolactone to give β-substituted propionic

Table I. Reaction of β-Propiolactone with Diorganocuprates[a]

R_2CuM	Product	Yield(%) glc	Yield(%) isolated	R_2CuM	Product	Yield(%) glc	Yield(%) isolated
Me_2CuLi		71	70	$t\text{-}Bu_2CuMgCl$		93	88
$Me_2CuMgBr$		89	86	($_2$CuMgBr		75	65
$n\text{-}Bu_2CuLi$		90	83	($_2$CuMgBr		88	87
$n\text{-}Bu_2CuMgBr$		100	92	Ph_2CuLi		20	20
$i\text{-}Pr_2CuMgBr$		80	79	$Ph_2CuMgBr$		86	80

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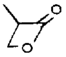
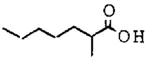
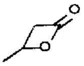
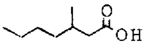
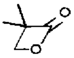
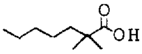
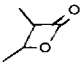
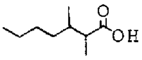
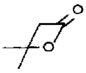
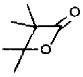
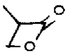
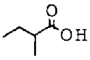
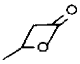
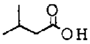
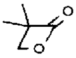
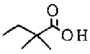
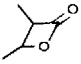
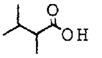
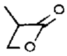
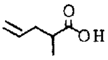
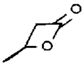
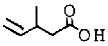
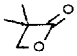
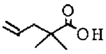
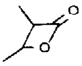
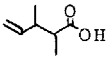
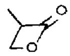
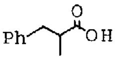
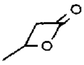
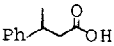
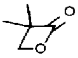
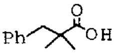
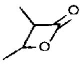
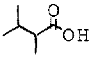
[a] All reactions were performed on 2 mmol scales at -30°C (1hr) and then 0°C (1hr) unless otherwise noted. A solvent system of THF-Me_2S (12:1) or THF was used for the reaction of R_2CuMgX or R_2CuLi, respectively. The molar ratio of R_2CuM and β-propiolactone is 1.1:1.0. The yields were based on β-propiolactone. [b] The reaction was carried out at -50°C (1hr) and then -20°C (1hr).

acids with new carbon-carbon bond in high yields, whether the substituent is primaly, secondary or tertialy carbon atom, or sp^2 carbon atom such as phenyl or vinyl group. Even allylcuprate, which is not so stable thermally, gave 5-hexenoic acid in a yield of 65%. The order of the reactivities of the organocuprates with various substituents for the reaction with β-propiolactone differs from that for the conjugate addition to enone.[6]

In order to confirm the scope and limitation of the ring opening reaction, the reaction of methyl-substituted β-propiolactones with diorganocuprates was examined as listed in Table II. In the case of bromomagnesium di-n-butylcuprate, β-methyl-β-propiolactone shows analogous reactivity, and α-methyl, α,α-dimethyl and α,β-dimethyl ones gave methyl substituted heptanoic acids in yields over

Table II. Reaction of Methyl-substituted β-Propiolactones with Diorganocuprates[a]

R in $R_2CuMgBr$	Lactone	Product	Yield[b] (%)
n-Bu-			85
n-Bu-			89
n-Bu-			82
n-Bu-			82
n-Bu-			0
n-Bu-			0
Me-			85
Me-			80
Me-			91
Me-			81
CH_2=CH-			72
CH_2=CH-			27
CH_2=CH-			48
CH_2=CH-			17
Ph-			52
Ph-			11
Ph-			3
Ph-			6

[a] All reactions were performed on 2 mmol scales with the same procedure as described in this letter. All products were identified by IR and NMR spectra. [b] Isolated Yields.

80%. β,β-Disubstituted β-propiolactones, on the contrary, such as β,β-dimethyl-β-propiolactone and α,α,β,β-tetramethyl-β-propiolactone, could not give the corresponding carboxylic acids, but gave decomposition products of the lactones. Above results were also observed in the case of the reactions of bromomagnesium dimethylcuprate. On the other hand, the reaction of the cuprates with sp^2 carbon atom, such as bromomagnesium divinylcuprate and diphenyl cuprate shows the decrease of the yields of the corresponding carboxylic acids: especially less than 30% yields of the carboxylic acids were obtained from β-methyl substituted β-propiolactones.

The following procedure for the synthesis of heptanoic acid is representative. n-Butylmagnesium bromide (1.0M in ether, 2.2 mmol) was slowly added to a solution of CuI (0.210g, 1.1 mmol) in 12 ml of THF and 1 ml of Me_2S at -30°C under argon atmosphere. The mixture was stirred for 30 min at -30°C. Then, a solution of β-propiolactone (0.144g, 2 mmol) in 2 ml of THF was added dropwise. The mixture was stirred for 1 hr and allowed to warm to 0°C for 1 hr. The reaction was quenched by addition of 3N HCl aq solution and then heptanoic acid was extracted with 3N NaOH aq solution from the organic layer. The alkaline solution was acidified, and extraction with ether and concentration gave pure heptanoic acid (92%).

This method of three carbon homologation thus appears to be of rather general utility and is particularly suited for the synthesis of α,α-disubstituted carboxylic acid from α,α-disubstituted β-propiolactone, in contrast with the conjugate addition of α,β-unsaturated acids. Thus, there are some advantages in the present reaction: these include that the reaction proceeds in highly regiospecific manner to provide a very useful method for the homologation with three carbon chain terminating with a carboxyl function, which can be easily transformed to various functional groups.[7]

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7. *Note Added in Proof.* An analogous result of the reaction of β-propiolactone with diorganocuprates was independently reported; J. F. Normant, A. Alexakis and G. Cahiez, *Tetrahedron Lett.*, 21, 935 (1980).

(Received in Japan 5 March 1980)