

**REACTION OF ORGANOMETALLIC COMPOUNDS
WITH PROPIOLACTONE**

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BY

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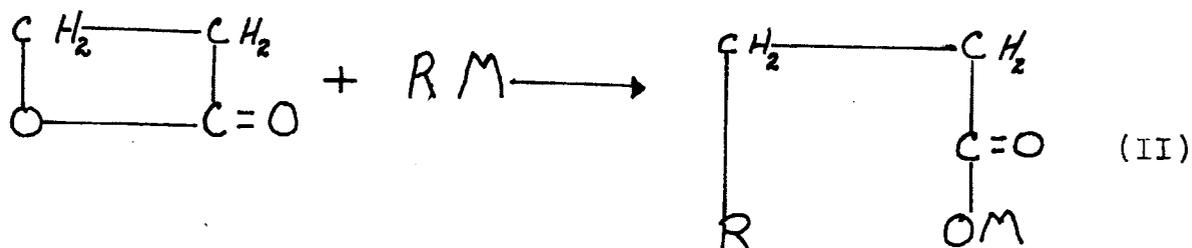
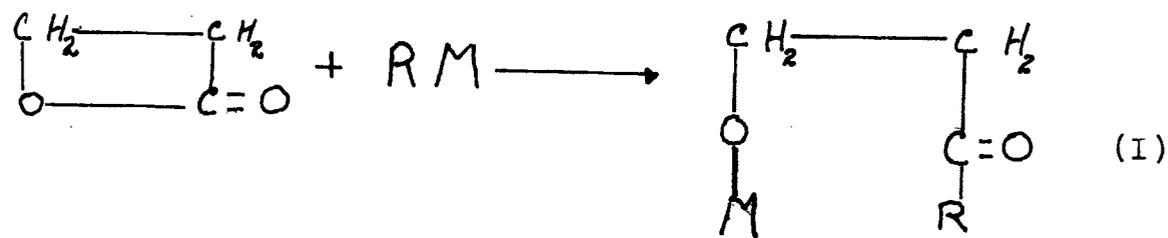
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INTRODUCTION

Studies by Gresham and Co-workers (7) have demonstrated the great ease with which the ring opening of propiolactone occurs at the acyl-oxygen or alkyl-oxygen bond. Polymerization of propiolactone is a competing reaction in most cases. An organometallic compound of the type RM might react with propiolactone in one of two ways:



Reaction (I) represents acyl-oxygen cleavage whereas (II) is the result of alkyl-oxygen cleavage.

Previous studies with phenyl magnesium bromide and benzyl magnesium bromide (8) showed that in addition to side reaction products, phenyl vinyl ketone and γ -phenyl butyric acid respectively were the major products. The former product was in all probability the result of acyl-oxygen cleavage, (reaction I), followed by dehydration of β -hydroxy propiophenone; whereas the latter was formed by simple alkyl-oxygen cleavage (reaction II).

The purpose of the present investigation was to study the reaction of other RM compounds with propiolactone. Particular emphasis centered on finding RM types that would give a general method for the synthesis of β -substituted propionic acids (reaction \square). The compounds studied were organometallic derivatives of lithium, cadmium, mercury, lead-sodium, lead-lithium, and tin-lithium.

EXPERIMENTAL

1. Phenyllithium

Phenyllithium (0.1 mole) was prepared by the procedure given in Organic Synthesis (1), by the action of lithium metal on bromobenzene in anhydrous ether. The phenyllithium solution was then cooled to 0°C in an ice-salt bath and propiolactone was added dropwise from a separatory funnel with vigorous stirring. A reaction occurred immediately to give a heavy white precipitate. After all the propiolactone was added, the mixture was decomposed with 35 cc. of water.

The water and ether layers were separated, and concentrated hydrochloric acid was added to the water layer until it was acidic to congo red paper. The water layer was then extracted with ether and the ether solution was dried over sodium sulfate. The ether was distilled off leaving a small amount of reddish oil which after cooling solidified yielding a rubbery material which could not be dissolved.

A heavy material precipitated from the above ether solution, the precipitate was filtered with suction and washed with ether. After drying, the weight of the product was 4.6 g. and melted at 135°C.

The Schotten-Baumann classification test was positive, indicating that there was a hydroxyl group present. The molecular weight of the material was determined by boiling point elevation using chloroform as the solvent. An experimental molecular weight of 225 was obtained. The molecular weight

of 1,1-diphenyl -1,3 propanediol is 228.

An authentic specimen of 1,1-diphenyl-1,3 propanediol was prepared as follows: To a mixture of 18.2 g. of benzophenone, 20 g. of ethyl bromoacetate in 90 cc. of benzene was added 8 g. of zinc. The mixture was refluxed for three quarters of an hour. The mixture was hydrolyzed with ice cold dilute H_2SO_4 . The benzene layer was separated and washed with dilute sulfuric acid. The benzene was evaporated off, leaving ethyl β -hydroxyl - β,β -diphenyl propionate, m.p. $87^\circ C$ (12). The ester group was reduced to a hydroxyl group by using lithium aluminum hydride in ether. The product of the reaction which was filtered and recrystallized from ethanol had a melting point of $134^\circ C$. A mixed melting point with the compound from the phenyllithium reaction showed no depression.

The ether layers from the original reaction yielded vinyl phenyl ketone, which was identified as the pyrrazoline (8).

2. Allylmagnesium Bromide

Gresham and Co-workers (8) received some acid when they reacted benzyl magnesium chloride with propiolactone. So it was decided to try to react allylmagnesium bromide with propiolactone which should act somewhat similar to the benzyl Grignard reagent, because of the similar positions of the double bonds.

Allylmagnesium bromide (0.1 mole) was prepared by the action of magnesium metal on allyl bromide in absolute ether. After the reaction was complete, the solution was cooled to

0°C and propiolactone was added dropwise. After all the propiolactone was added, the precipitate was dissolved in a water solution of ammonium chloride and the two layers were separated and concentrated HCl was added to the water layer yielding an oil. The oil was extracted with two 100 cc.-portions of ether and dried over sodium sulfate. The ether was then distilled off, leaving 6.2 g. , 54.4%, of β -allyl propionic acid boiling at 202°C. Density: 1.01, Neut. Eq.: 111 (11).

3. Cadmium Compounds

It is known that cadmium compounds are less reactive with carbonyl groups than lithium compounds or Grignard reagents, so this type of compound was studied next.

The cadmium compound is made from the Grignard reagent, by adding anhydrous cadmium chloride to the ether-Grignard solution.

a) Bromobenzene

Phenylmagnesium bromide (0.1 mole) was prepared as above and 18.2 g. (0.1 mole) of cadmium chloride was added slowly with stirring. After the reaction was complete, the ether solution was decanted into another flask, 5 cc. of this ether solution was added to 50 cc. of water and titrated with 0.1 N HCl using methyl orange as an indicator. The total volume of the solution was determined and the amount of the cadmium compound still present was thus determined. The best yield in converting the Grignard reagent to the cadmium compound was 50%.

The ether solution of the organocadmium compound (0.05 mole) was cooled to 0°C and 0.05 mole of propiolactone was added dropwise with stirring, yielding a heavy white precipitate. Water was added after the reaction was complete and the precipitate dissolved.

The two layers were separated and HCl was added to the water layer. The water layer was extracted with two 100 cc.-portions of ether, and the ether layers were dried over sodium sulfate. The ether was distilled off leaving a yellow liquid which solidified. The solid was recrystallized from petroleum ether yielding 5.8 grams of white plate-like crystals. Qualitative tests were negative for halogens.

The yield of β -phenyl propionic acid based on phenylcadmium bromide was 77.3%. The melting point was 48.5°C and the neutralization equivalent, 148 (9).

Using the same general procedure other organocadmium compounds were studied. The results are summarized in Table 1.

TABLE 1

Results of Reaction of Organo-Cadmium Compounds with Propiolactone.

<u>HALIDE</u>	<u>PRODUCT</u>	<u>MELTING POINT °C</u>	<u>YIELD %</u>	<u>NEUT. EQUIV.</u>
m-Bromotoluene	β -(m-tolyl)propionic acid	45(10)	51.2	160
2-Iodothiophene	β -(2-Thiophene)propionic acid	128	40.1	155
n-Butylbromide	Heptanoic	B.P. 222(13)	51.3	127

4. Diphenyl Mercury

a) Preparation

Phenyl diazonium chloride-mercuric chloride (2): To 450 cc. of conc. hydrochloric acid and 500 cc. of water, in a gallon container equipped with a stirrer, is added 91.12 cc. (1 mole) of aniline. The solution was cooled by the addition of 500 g. of ice, when the temperature reached 5°C, solid sodium nitrate (69 gr.) was added. After the reaction was complete, a solution of 271 g. of mercuric chloride dissolved in 300 cc. of conc. HCl mixed with 300 g. of ice was added. A heavy precipitate was formed, and was filtered and washed with two 400 cc.-portions of water and two 150 cc.-portions of acetone and allowed to dry at 20°C.

Diphenyl mercury (3): In a liter-round bottomed flask, equipped with a stirrer, was placed 205.5 grams (0.5 mole) of the above compound, 700 cc. of acetone and 189 g. (3 moles) of copper powder. The mixture was cooled to 20°C and stirred for one hour. Seven hundred cc's of conc. NH₃ Aq. solution was added, mixed well, and allowed to stand over night. The liquid was decanted, and the solid was filtered and washed with 25 cc.-portions of water, acetone, and ether. After drying, the crude diphenyl mercury was recrystallized from xylene.

b) Diphenyl mercury (0.05 mole) was dissolved in nitromethane and was cooled to 0°C. Propiolactone (0.1 mole) was added dropwise, yielding no white precipitate. The nitromethane was distilled off leaving the diphenyl mercury crystals.

This indicated that no reaction had taken place.

5. Triphenyllead Sodium

To a solution of 100 cc. of liquid ammonia in 155 cc. of anhydrous ether was added 0.561 g. (0.0244 moles) of sodium. When the sodium was completely dissolved, 6.428 g. (0.0122 moles) of tetraphenyl lead was added (solid because of its insolubility in ether) to the dark blue solution. The resulting straw-yellow solution was stirred until all of the excess ammonia had evaporated and the reaction flask had come to room temperature.

The yellow solution was slowly filtered into another flask through a system protected from atmospheric moisture. To the cooled (0°C), stirred filtrate was added 0.0122 mole of propiolactone. The solid material was filtered off and was suspended in a dilute HCl solution and stirred vigorously. The suspension was filtered and the residue was crystallized from 95% ethanol.

In this manner there was obtained 1.26 g. of solid material melting at 213-214°C. Anal. calcd. for $C_{21}H_{20}O_2Pb$: Pb, 40.6%. Found: Pb 41.2%.

6. Triphenyllead Lithium

The same procedure for the preparation of triphenyllead lithium was used as given by Gillman, Summers and Leeper (6).

To a well stirred suspension of 15.85 g. (0.057 moles) of finely ground, anhydrous lead chloride in 50 cc. of ether

maintained at -10°C , was added dropwise, 0.17 moles of phenyllithium dissolved in 137 cc. of ether. After the reaction was complete, 5 cc. of the above solution was added to 50 cc. of water and titrated with 0.1 N HCl.

Triphenyllead lithium (0.04 mole) was reacted with 0.04 moles of propiolactone at 0°C . The precipitate was suspended in dilute HCl and stirred vigorously. The solution was filtered yielding 4.2 g. of a white solid material, melting at 213°C . A mixed melting point of this compound and the one from triphenyllead sodium showed no depression.

The methyl ester of the acid was made by the addition of some of the compound to an ether solution of diazomethane. This gave a white solid compound melting at 186°C .

7. Triphenyltin Lithium

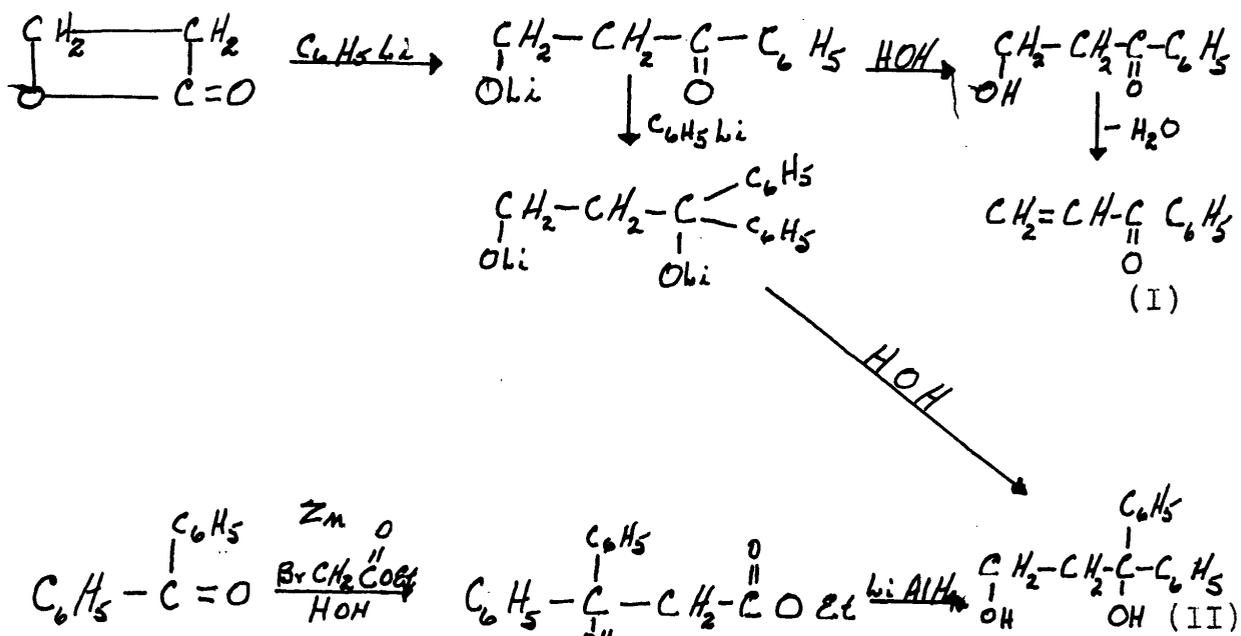
To a well stirred suspension of 10.81 g. (0.057 moles) of finely ground, anhydrous stannous chloride in 50 cc. of ether maintained at -10°C , was added dropwise, 0.170 moles (3 equivalents) of phenyllithium dissolved in ether. This was handled the same as above to find the correct amount of the compound present.

To a cooled (0°C) solution of triphenyltin lithium (0.05 moles) was added dropwise 0.05 moles of propiolactone. The white solid compound which separated was suspended in dilute HCl and stirred vigorously. The yellow solid was filtered, and recrystallized from hot ethanol. The weight of the product was 6.6 g. and the melting point was 202°C .

An attempt to make the methyl ester as above yielded only starting material. This fact together with the yellow color of the product indicated that the compound might be triphenylstannyl vinyl ketone. An alcohol solution of the compound was refluxed with phenylhydrazine. Addition of water to the alcoholic solution yielded a white precipitate melting at $168 - 9^{\circ}\text{C}$. The material gave a positive qualitative test for nitrogen. Anal. calcd. for $\text{C}_{21}\text{H}_{18}\text{O Sn}$: Sn, 29.3%. Found: Sn, 29.1%.

CONCLUSION

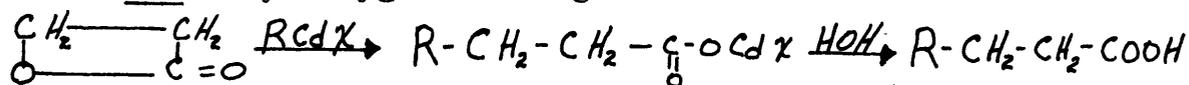
Phenyllithium reacts with propiolactone to yield a mixture of vinyl phenyl ketone (I) and 1,1-diphenyl-1,3-propanediol (II)



The structure of (II) was established by an independent synthesis involving the reduction of ethyl 3,3-diphenyl-3-hydroxy propionate with lithium aluminum hydride. Isolation of vinyl phenyl ketone from the reaction of propiolactone with phenyllithium indicates that (II) was formed by acyl-oxygen cleavage of propiophenone followed by the addition of a second mole of RLi to the carbonyl linkage of the lithium alkoxide of the intermediate hydroxy ketone. This reaction affords a convenient synthesis of heretofore unreported 1,1-substituted-1,3-propanediols.

Organocadmium compounds, aromatic as well as aliphatic, react with propiolactone to yield 3-substituted propionic

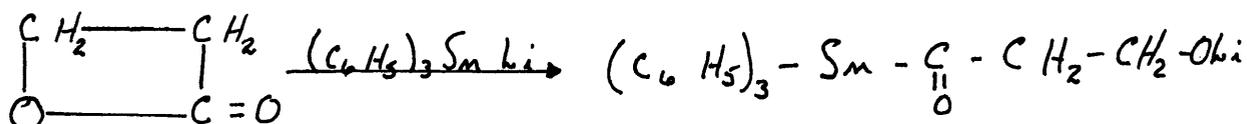
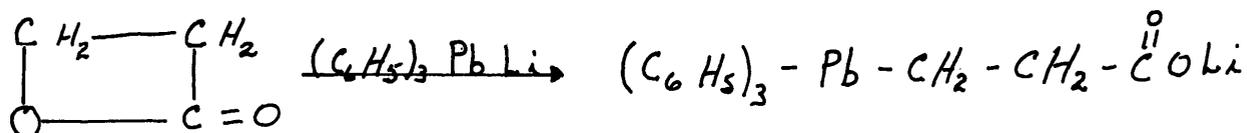
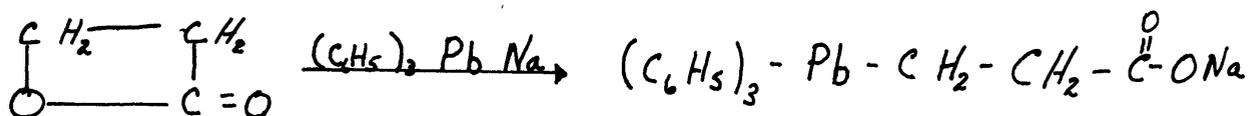
acids via alkyl-oxygen cleavage of the lactone.



The reaction appears to be general in nature, subject to limitations imposed by the well known instability of the precursory Grignard reagent towards certain functional groups. The relative merits of the present method for preparing 3-substituted propionic acids over such classical procedures as the Perkin reaction, the Reformatsky reaction, the Knoevenagel condensation and the Arndt-Eistert synthesis must be judged on the bases of the availability of starting materials and the functional groups present. A noteworthy point is that the present method starts with a halogen derivative and introduces a three carbon chain directly, whereas the other methods utilize a carbonyl or carboxyl substituent and lengthen the chain by two carbon atoms.

Diphenylmercury is inert toward propiolactone.

Triphenyllead sodium and triphenyllead lithium react with propiolactone to yield the corresponding propionic acids, whereas, the triphenyltin lithium reacts to give the unsaturated ketone.



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