

On the Reaction between Methylithium and Carboxylic Acids

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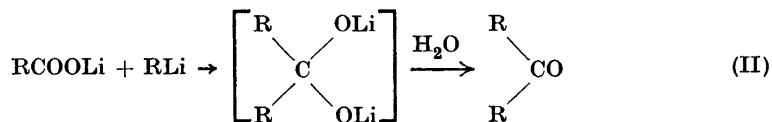
The aim of this work was to investigate the possibilities of preparing methyl ketones by the action of methylithium on different carboxylic acids. The methyl ketones have for many reasons been of great interest to prepare, *i.e.* for subsequent oxidative degradation according to Krafft¹. For the ketone synthesis Krafft¹ used the distillation of the barium salt of the unknown acid together with barium acetate. However, the yields by this method are in general low.

The action of Grignard compounds on carboxylic acids² and their derivatives³ has also been tried. The derivatives of acids having a double bond in β - γ -position have, however, offered some difficulties.

In 1933, Gilman and van Ess⁴ showed that on carbonation phenyllithium yielded 70% benzophenone and no benzoic acid, which is the main product on carbonation of the corresponding magnesium compound. They found that the reason for the high yield of ketone was the higher reactivity of the organolithium compound. If an aryllithium compound was allowed to react with carbon dioxide at temperatures between -50 — -80°C the following reaction occurred



At a higher temperature (room temperature) another reaction took place. To the lithium salt of I was added one mole of aryllithium, and a dilithium salt of a dihydroxymethane was obtained, which on hydrolysis yielded a ketone in accordance with the following general reaction.



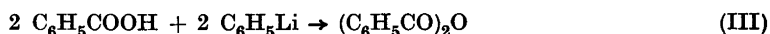
Gilman and van Ess ⁴ (compare Moureu and Delange ⁵) also showed that it was possible to prepare mixed ketones in an analogous reaction.

In a paper on the preparation of substances related to vitamine A, Arens and van Dorp ⁶ describe the preparation of the C₁₈-ketone by the action of methyllithium on β -ionylidene crotonic acid. The reaction was instantaneous and the yield was over 90 %. It may be noticed that no addition to the double bonds occurred in this synthesis. Other authors have obtained similar results ⁷⁻¹⁰.

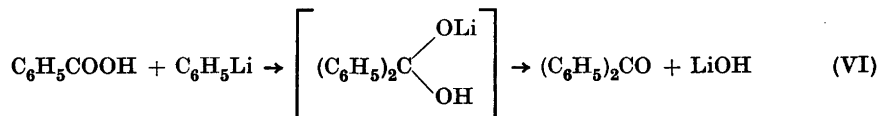
An other methyl ketone ¹¹ has been obtained in a yield of 90—95 % by the interaction of methyllithium with lithium cinnamate.

Only in one case, hitherto, has any comparison been made between the use of the free acid or its lithium salt: In the case of benzophenone Gilman and van Ess ⁴ have made two syntheses. One started with the lithium benzoate, which was allowed to react with one mole of phenyllithium, and was found to give a 70 % yield of ketone and no tertiary alcohol; the second experiment started with benzoic acid and two moles of phenyllithium and yielded 37.2 % of ketone and 14.1 % of triphenylcarbinol.

Two possible explanations are given for the formation of the tertiary alcohol. The first is that benzoic acid is dehydrated by phenyllithium to give benzoic anhydride. This would react with one mole of phenyllithium to give lithium benzoate and "free" benzophenone, which would enter the ordinary reaction of a ketone yielding triphenylcarbinol



Another explanation is suggested, in which the phenyllithium is supposed to be added directly to the carbonyl bond (without previous formation of lithium salt) yielding an intermediary product (VI), which by phenyllithium is brought over into the alcohol in accordance with the reaction V above.



When using methyllithium, however, these side reactions are not likely to occur, because of the markedly lower reactivity of methyllithium as compared with phenyllithium, unless the concentration of methyllithium is strongly increased. Karrer *et al.*⁷ have shown that when one mole of β -ionylidene crotonic acid is allowed to react with two moles of methyllithium only ketone is formed. If the number of moles of methyllithium is increased to five, equal quantities of ketone and carbinol are obtained, and by a further increase of methyllithium to ten moles per mole acid, the tertiary alcohol will be formed almost exclusively. In the case of the two higher concentrations the explanations given

by Gilman and van Ess⁴ seem very probable. The side reaction of carbinol formation may be avoided by adding the methyl lithium solution to the acid, thus avoiding too high concentrations of methyl lithium.

To compare the difference in yield when using the free acid or the lithium salt of the acid, experiments have been carried out with cinnamic acid. A series of syntheses was carried out, the results of which are compiled in Table 1.

Table 1. Yield of methyl ketone on refluxing cinnamic acid/lithium cinnamate with methyl lithium during different number of hours. (*h* = time of reflux in hours).

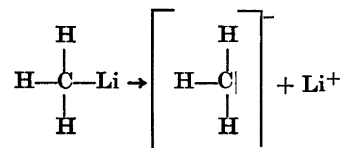
Reactant	<i>h</i>	Yield in %
Cinnamic acid	0	77
Lithium cinnamate	2	69
„ „	6	79

It appears that slightly higher yields were obtained by using the lithium salt. However, as the lithium salts in some cases are difficult to obtain, all syntheses have been carried out with the free acid.

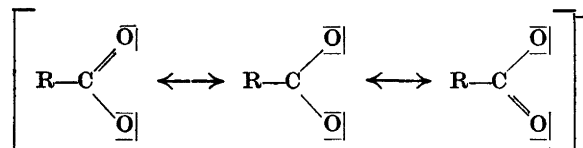
In a series of runs methyl lithium was allowed to react with different acids. In Tables 2—5 the yields of methyl ketone have been collated.

The mechanism of the formation of a ketone may be explained in the following way:

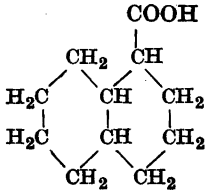
In methyl lithium there is, as in the other organometallic compounds, a displacement of electrons towards the carbon atom, with the formation of a carbanion with a free electron pair and a positive lithium ion.



The lithium salt of a carboxylic acid has the following resonance structures

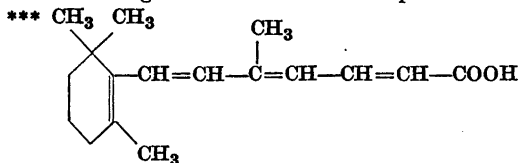


Tables 2-5. Yields of methyl ketones obtained by the reaction of methyllithium with different acids.

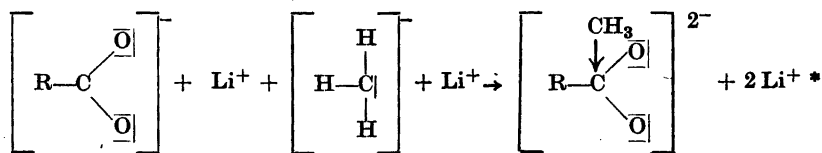
Acid	Yield in %	Acid	Yield in %
CH ₃ COOH	0	H-CH ₂ COOH	0
CH ₃ CH ₂ COOH	~ 1	CH ₃ -CH ₂ COOH	~ 1
CH ₃ (CH ₂) ₄ COOH	83	CH ₃ O-CH ₂ COOH	16
CH ₃ (CH ₂) ₁₀ COOH	63	C ₆ H ₅ -CH ₂ COOH	76
	90 *		
Acid	Yield in %	Acid	Yield in %
C ₆ H ₅ COOH	82	C ₆ H ₅ -CH ₂ CH ₂ COOH	100
C ₆ H ₅ CH ₂ COOH	76	C ₆ H ₅ -CH=CH-COOH	77
C ₆ H ₅ CH ₂ CH ₂ COOH	100	C ₁₇ -acid ***	> 90**

* According to Mannerskantz, C., private communication.

** According to Arens and van Dorp ⁶.



On the addition of methyllithium to the lithium salt of a carboxylic acid, the carbanion with its unshared electron pair adds to the sextet of the carboxy-



* Concerning the degree of polarity of the Li-O bond, little is known.

lic acid anion, with the formation of a new carbon-carbon bond, and the oxygen with one of its unshared electron pairs forms a bond with the lithium atom. The dilithium salt of the dihydroxymethane thus obtained is hydrolysed by water to give the methyl ketone.

Of decisive importance for the addition, and thereby for the yield, is the formation of the carbonium ion of the carboxylic acid, which in its turn depends on the nature of the radical R- of the acid RCOOH¹².

In Table 2 some saturated acids have been investigated. It appears that the yield of methyl ketone is satisfactory when the radicals of the acids contain more than 5 or 6 carbon atoms, and that lower acids react incompletely or not at all. The cause of the increasing yield by lengthening the radical may be seen in the electron-repelling effect of the methyl group, an effect which is weakened by inserting methylene groups.

In Table 3 experiments with substituted acetic acids have been compiled. Here the influence of the phenyl and methoxyl groups may be specially noticed. In view of the electron-attracting properties of these groups, it might easily be thought the addition would take place. However, the yield with the methoxyacetic acid seems exceptionally low.

In Table 4 the weakening effect of the methylene group on the electron-attracting effect of the phenyl group may be seen. With hydrocinnamic acid, where a quantitative yield has been obtained, the synthesis has been repeated, and the yield was found to be correct. No tertiary alcohol could be found.

From Table 5 it appears that a certain stabilizing action is exerted by the double bond in the cinnamic acid, but no addition to double bond occurs, not even in such highly conjugated systems as in the C₁₇-acid.

In conclusion it may be said that the preparation of methyl ketones by the action of methyllithium on carboxylic acids generally gives excellent yields, and that no interference with double bonds occurs. As a rule acids having an electron-attracting group seem to give a higher yield of ketone than those containing an electron-repelling group.

EXPERIMENTAL

Preparation of methyllithium

The preparation of methyllithium was carried out in the apparatus shown in Fig. 1, a three-necked flask equipped with a dropping funnel (50 ml), a reflux condenser with a mercury trap, a Hershberg stirrer with a mercury seal and a gas inlet tube.

For the preparation of methyllithium three methods were tried, one using methyl chloride and two with different ratios of methyl iodide/lithium metal. When using methyl chloride¹³ the yields varied between 20–50 %.

Using the more easily handled methyl iodide Gilman *et al.*¹⁴ give two different ratios for the concentration of methyl iodide/lithium metal, 1.25/1.0 and 1.0/2.2; both said to yield similar results. However, in the authors experiments the latter ratio has been found to give higher yields, and has therefore been used in this work. (With the ratio 1.25/1.0 the yields were 75–80 %, and with the ratio 1.0/2.2 90–95 % yields were obtained.)

An example of a preparation using the latter ratio is given below:

0.35 mole (2.4 g) of lithium sand, prepared according to Perrine and Rapoport¹⁵, was brought into the reaction vessel with 100 ml of ether*. The air in the apparatus was then expelled with nitrogen gas, previously dried over calcium chloride, phosphorus pentoxide and soda asbestos ("Ascarite"). The Hershberg stirrer was started, and the stream of nitrogen was slowed down. The speed of the gas flow could be noticed at the mercury trap, which also served to give a slight overpressure to exclude moisture, oxygen and carbon dioxide.

To the lithium metal was added 1 ml of methyl iodide, and the reaction was started by carefully heating on a water bath. When the reaction began the water bath was removed and another 100 ml of ether was added, and 0.16 mole (23 g) of methyl iodide diluted with 75 ml of ether was then introduced at such a rate as to cause gentle reflux. After all the methyl iodide had been added the mixture was refluxed on a water bath for 1 hour, after which time the stirrer was stopped and the solution allowed to cool. The unreacted lithium metal then rose to the surface and a greyish white precipitate of lithium iodide and metallic lithium settled at the bottom of the flask, leaving a weakly opalescent solution between. Samples of the solution were taken and after hydrolysis with water titrated with 0.1 N hydrochloric acid. Yield 0.15 mole of methyllithium (230 ml 0.67 N methyllithium solution; 96 %).

As there is no exact method of determining the concentration of methyllithium, only small amounts were prepared and were used in the coupling reaction immediately after the preparation.

Preparation of methyl ketones using the free acid

For the coupling reaction between methyllithium and carboxylic acids an apparatus was used consisting of a round-bottomed flask (250 or 100 ml) with a side tube for a gas inlet capillary and equipped with a reflux condenser protected by a sodium hydroxide drying tube. The reaction was carried out in a nitrogen atmosphere, the nitrogen gas being dried over calcium chloride, phosphorus pentoxide and soda asbestos. The coupling was carried out according to the following general scheme:

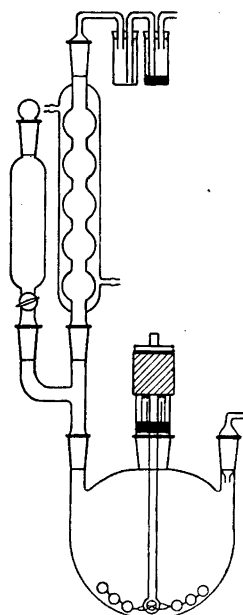


Fig. 1. Apparatus used for the preparation of methyllithium (description see text).

* The ether has always been dried with sodium wire.

0.03 mole of the acid dissolved in 50 ml of ether was brought into the reaction vessel, and the air was then expelled with a rapid stream of nitrogen. After 2–3 minutes the gas stream was slowed down, just to create sufficient bubbles for stirring the solution during the experiment.

When all air had been expelled 0.06–0.07 mole of an ethereal solution of methyl-lithium was added through the condenser. A vivid reaction took place, the ether refluxed, and a white precipitate was formed (lithium salt of the acid). After the addition of all the methyl-lithium the precipitate sometimes dissolved and a weakly opalescent solution was obtained. If necessary, the solution was then refluxed for 10–30 minutes to complete the reaction. After the solution had reached room temperature, water was slowly added. The excess of methyl-lithium was thus destroyed and lithium hydroxide was formed from the intermediate dilithium salt of the dihydroxymethane.

The alkaline water layer, which contained the lithium salt of unreacted acid, was removed in a separatory funnel, and the ethereal layer washed three times with half its volume of water. The ether solution was then dried over magnesium sulphate, filtered and the ether driven off, first at ordinary pressure and then at 8–10 torr. The ketone was purified if necessary, which however was seldom the case. If needed, derivatives were prepared for characterisation of the ketone.

The acids which have been investigated were coupled with methyl-lithium in a series of runs. The experiments and the isolation of the methyl ketones were carried out according to the general scheme above. Any deviations from this will be given in the case of the individual acids below.

Acetic acid. 5 g of glacial acetic acid was diluted with 100 ml of ether and the solution was dried over magnesium sulphate, and then filtered.

To 0.023 mole (14 ml of the above solution) of acetic acid was added 15 ml of ether and 0.050 mole of methyl lithium. The solution was boiled under reflux for 1 hour. After hydrolysis with water the ethereal solution was shaken five times, with 20 ml of water each time. The water solutions were mixed and after adjustment of pH to ~ 8 , they were distilled. The first fraction, 1 ml, was collected. No acetone could be identified. Yield 0%.

Propionic acid. 0.027 mole (2.0 g) of propionic acid diluted with 30 ml of ether was allowed to react with 0.058 mole of methyl-lithium. The isolation was carried out in analogy with that of acetic acid. A 1 ml fraction, which had a faint-smell of 2-butanone, was collected. From the 1 ml fraction 20–30 mg of the 2,4-dinitrophenylhydrazone was precipitated. Yield $\sim 1\%$.

Caproic acid. 0.035 mole of caproic acid in 50 ml of ether was coupled with 0.075 mole of methyl-lithium. A white precipitate was first formed but dissolved in a few minutes. The solution was boiled under reflux for 5 minutes, after which time it was opalescent. The isolation of the ketone gave 3.3 g of a weakly yellow liquid; b.p. 149°; yield 83% 2-heptanone.

Lauric acid. To 0.020 mole (4.0 g) of lauric acid dissolved in 30 ml of ether was added 0.044 mole of methyl-lithium. The solution was boiled under reflux for 1 hour, when the precipitate first formed partly dissolved. Isolation gave 2.5 g of 2-tridecanone; m.p. $\sim 25^\circ$. 2,4-dinitrophenylhydrazone from alcohol m.p. 68° corr.; yield 63%.

Cinnamic acid. To a solution of 0.0088 mole (1.3 g) of cinnamic acid in 50 ml of ether was added 0.018 mole of methyl-lithium. The yield of benzalacetone was 1.0 g. 2,4-dinitrophenylhydrazone from alcohol m.p. 226–227° corr.; yield 77%.

Methoxyacetic acid. Methoxyacetonitrile was prepared¹⁶ and hydrolysed. On purification by distillation *in vacuo* a fraction of constant boiling point was collected; b.p. 96°/13 torr; $n_D^{20} = 1.4168$.

0.043 mole of methyllithium was added to 0.020 mole (1.8 g) of methoxyacetic acid in 50 ml of ether. A weakly yellow precipitate was formed, which partly dissolved on boiling under reflux for 30 minutes. Isolation of the ketone yielded 0.27 g of methoxyacetone; yield 16 %.

Hydrocinnamic acid. 0.050 mole (7.5 g) of hydrocinnamic acid was dissolved in 50 ml of ether and was allowed to react with 0.12 mole of methyllithium. The solution was boiled under reflux for 1 hour. 7.5 g benzylacetone was obtained; yield 100 %. (Test for tertiary alcohol was negative.)

Benzoic acid. A solution of 0.027 mole (3.3 g) of benzoic acid in 50 ml of ether was coupled with 0.055 mole of methyllithium. On isolating the ketone, the water layer was extracted twice with 50 ml of ether and the ethereal solutions were treated according to the general scheme. 2.7 g of acetophenone was isolated; yield 82 %.

Phenylacetic acid. 0.026 mole (3.5 g) of phenylacetic acid was allowed to react with 0.055 mole of methyllithium. A white precipitate separated, which partly dissolved. Isolation gave 2.65 g of phenylacetone; yield 76 %.

Preparation of methyl ketone using the lithium salt

Cinnamic acid was dissolved in the calculated amount of 1.98 *N* lithium hydroxide in water. The solution was evaporated to dryness and the solid residue finely divided in a mortar. The lithium salt was then washed with ether and dried at 120° for 10 hours.

To a suspension of 0.013 mole of finely divided lithium cinnamate in 25 ml of ether was added 0.015 mole of an ethereal methyllithium solution. On refluxing for 2 hours the main part of the salt had reacted. Isolation (as above) of the ketone gave 1.3 g of benzalacetone; yield 69 %.

In another run the time of reflux was increased to 6 hours. In this case the yield was 79 %.

SUMMARY

1. Methyllithium has been prepared in a nitrogen atmosphere in yields between 90—95 %.
2. Comparison has been made between the lithium salt of an acid and the free acid in the preparation of methyl ketone. No differences in yield have been obtained.
3. The preparation of methyl ketones by the action of methyllithium on carboxylic acids has been shown to give generally excellent yield.

I wish to express my sincere gratitude to Professor Karl Myrbäck and Docent Nils Löfgren for invaluable aid and discussions.

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