

Condensation of Ketones and *t*-Butyl Chloroacetate in the Presence of Magnesium.

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(Received November 20, 1965)

Condensation of *t*-butyl chloroacetate and ketones by means of magnesium in ether or benzene alone was carried out but the excellent yields of β -hydroxy ester could not be obtained, and the results of the condensation of *t*-butyl bromoacetate and ketones by means of magnesium and mercuric chloride in benzene were also disappointing.

When a mixture of benzene and ether was used as solvent in the condensation of *t*-butyl chloroacetate and ketone in the presence of magnesium and mercuric chloride, the yields of β -hydroxy esters from cyclohexanone and methyl isobutyl ketone were 62 and 71% respectively, and were comparable with those of other condensing methods.

A number of researches¹⁾ has been made on the Reformatsky reaction with chloroesters which have the advantage of lacking the lachrymatory property usually associated with the bromoesters. However, the yields of β -hydroxy esters obtained by methyl or ethyl chloroacetate are considerably lower than those realized by the brominated analogs. It is reported that various additive agents^{2,3)} such as copper powder have been used for accelerating the reaction but the successful results could not be obtained except of the condensation of benzaldehyde with α -chloroester¹⁾.

On the other hand, β -hydroxy ester can be scarcely obtained as condensation product when magnesium was used as condensing agent in the Reformatsky reaction, which is considered more reactive than zinc. Nord et al.¹⁾ tried to add mercuric halides as additive agents and obtained methyl β -methylcinnamate in a 68% yield from

acetophenone and methyl chloroacetate in the case of mercuric bromide. Henbest et al.⁴⁾ recommended to add mercuric chloride when the practice of reaction is difficult.

It may be expected that the condensation of ketones and chloroacetate in the presence of magnesium is performed by excellent yield by the use of *t*-butyl chloroacetate as ester component, since it prevents the formation of β -keto ester by the self-condensation of α -haloester itself⁵⁾. Thus, to a mixture of magnesium and ether there was added a few drops of methyl iodide, then an ethereal solution of *t*-butyl chloroacetate and ketone. The reaction mixture was decomposed with dilute acid. Since β -hydroxy esters could not be obtained in the reaction, a small amount of iodine was added to accelerate the reaction before a mixture of ketone and *t*-butyl chloroacetate was added. The results are summarized in Table I. In the case of aceto-

Table I Condensation of *t*-Butyl Chloroacetate with Ketones

Ketone	Product	Yield, %	M. p. or B. p., °C			
			Found	Mm.	Reported ⁶⁾	Mm.
Acetophenone	<i>t</i> -Butyl β -hydroxy- β -phenylbutyrate	48	138—145	8	125—126	6
Benzophenone	<i>t</i> -Butyl β -hydroxy- β , β -diphenylpropionate	45	M. p. 92—92.5		92—92.2	
Methyl Isobutyl Ketone	<i>t</i> -Butyl β -hydroxy- β -isobutylbutyrate	44	122—128	22—23	114—115	18
Benzalacetone	<i>t</i> -Butyl β -methyl- β -styrylacrylate	35	135—140	2	160—165	5

phenone, benzophenone and methyl isobutyl ketone, the yields of *t*-butyl β -hydroxy esters were 48, 45 and 44% respectively. When a benzalacetone was used as ketone, α , β -unsaturated ester was obtained, as in the case of *t*-butyl bromoacetate⁶⁾, in a 35% yield.

In some cases these results were better than those reported. Thus, the condensation of *t*-butyl chloroacetate with acetophenone and benzophenone was realized in yields of 48 and 45% respectively, whereas the Reformatsky reaction using ethyl chloroacetate has been reported to produce β -hydroxy esters in yields of 40 and 30% respectively²⁾. Nord et al.¹⁾ obtained methyl β -methylcinnamate in a 68.3% yield, by the dehydration of the condensation product, from acetophenone and methyl chloroacetate using magnesium and mercuric bromide as condensing

agent.

By heating the reaction mixture to the boiling point the Reformatsky condensation can be effected in shorter time, and the use of a mixture of equal amount of benzene and toluene, which permits refluxing at temperature between 90° and 105°, is especially advantageous when the carbonyl component is a ketone⁷⁾. It is expected that the use of benzene in place of ether as solvent is effected in the condensation between *t*-butyl bromoacetate and ketone, but the excellent results could not be obtained. Thus the present author added mercuric chloride as additive agents as Nord¹⁾ had done. These results, summarized in Table II, cannot bear comparison with those realized in the case of ether as solvent. Similar results were obtained in the case of *t*-butyl chloroacetate.

Table II Condensation of *t*-Butyl Bromoacetate with Ketones by Means of Magnesium and Mercuric Chloride in Benzene

Ketone	Product	Yield, %	B. p., °C			
			Found	Mm.	Reported ⁶⁾	Mm.
Acetophenone	<i>t</i> -Butyl β -hydroxy- β -phenylbutyrate	59	142	8	125—126	6
Cyclohexanone	<i>t</i> -Butyl 1-hydroxy-cyclohexylacetate	33	113—114	8	125—127	13
Methyl Isobutyl Ketone	<i>t</i> -Butyl β -hydroxy- β -isobutylbutyrate	61	99—100	10	114—115	18
Benzalacetone	<i>t</i> -Butyl β -methyl- β -styrylacrylate	37	142—145	3	160—165	5

When a mixture of benzene and ether was used as solvent in the case of *t*-butyl chloroacetate, yields of β -hydroxy esters from cyclohexanone and methyl isobutyl ketone were comparable with those of corresponding β -hydroxy esters obtained by another method. Thus, the condensation of *t*-butyl chloroacetate with cyclohexanone and methyl isobutyl ketone were realized in yields of 62 and 71% respectively, whereas the condensation of *t*-butyl bromoacetate with cyclohexanone and methyl isobutyl ketone in ether was realized in 80 and 78% yield respectively⁶⁾.

On the other hand, Vul'fson⁸⁾ reported that the yields of β -hydroxy esters are increased by adding thiophene to benzene when the Reformatsky condensation is carried out in benzene. From this report and our results it might be concluded that the presence of solvent possessing lone electron pair accelerates the formation of enolate anion of ester to increase the yields

of β -hydroxy esters.

Experimental^{*)}

***t*-Butyl chloroacetate** was prepared by the action of chloroacetyl chloride^{**)} on *t*-butyl alcohol in the presence of dimethylaniline⁹⁾.

The product, which was obtained in a 65% yield, b. p. 51—52°/11 mm. (lit.⁹⁾ b. p. 48—49°/11 mm.), when shown to be acidic, was washed with saturated sodium bicarbonate solution and distilled in the presence of a trace of magnesium oxide.

*) All melting and boiling points are uncorrected.

***) In a cooled flask, 120 g. of chloroacetic acid was placed and 200 g. of thionyl chloride was then added all at once. The resulting mixture was allowed to stand at room temperature for 1 hr. and refluxed for 6 hr. to complete the reaction. The excess of thionyl chloride was distilled through a column and the residue was distilled subsequently. The yield of chloroacetyl chloride boiling at 104—105° was 129 g. (92%).

Condensation of Acetophenone and *t*-Butyl Chloroacetate by Means of Magnesium in Ether. — To a mixture of 2.0 g. of magnesium, a piece of iodine and 30 ml. of anhydrous ether there was added a few drops of methyl iodide. When the reaction had started, a solution of 6.0 g. of acetophenone and 7.8 g. of *t*-butyl chloroacetate in 20 ml. of ether was added with stirring and a piece of iodine was added to the resulting mixture. After the mixture was refluxed for 2 hr., it was decomposed with 10% sulfuric acid and ice. The organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with saturated sodium bicarbonate solution and with water, dried over anhydrous sodium sulfate and the solvent was removed. The residue was distilled in the presence of a trace of magnesium oxide, and *t*-butyl β -hydroxy- β -phenylbutyrate (5.6 g. 48% yield) was obtained as a pale-orange oil, b. p. 138–145°/8 mm. Reported b. p. is 111–112.5°/2 mm¹⁰⁾ and 125–126°/6 mm⁶⁾.

The other *t*-butyl β -hydroxy esters cited in Table I were prepared similarly.

Condensation of Acetophenone and *t*-Butyl Bromoacetate in Benzene by Means of Magnesium and Mercuric Chloride. — A mixture of 2.0 g. of magnesium, 0.2 g. of mercuric chloride and 30 ml. of anhydrous benzene was heated to reflux and a few drops of a mixture of acetophenone and *t*-butyl bromoacetate was added. When the reaction had started, a solution of 6.0 g. of acetophenone and 10.0 g. of *t*-butyl bromoacetate in 30 ml. of benzene was added over a 60-min. period. Stirring was then continued for 200 min. at the boiling point of the mixture. After cooling the contents were decomposed with 10% sulfuric acid and treated in the same manner as described above. Distillation gave *t*-butyl β -hydroxy- β -phenylbutyrate in a 59% yield.

The other *t*-butyl β -hydroxy esters cited in Table II were prepared similarly.

Condensation of Acetophenone and *t*-Butyl Chloroacetate in Benzene. — A few drops of methyl iodide was added to a mixture of 2.0 g. of magnesium and a piece of iodine in 30 ml. of benzene, and heated to the boiling point. When

the reaction had started, a solution of 6.0 g. of acetophenone and 7.7 g. of *t*-butyl chloroacetate in 20 ml. of benzene was added over a 25-min. period and refluxed for 100 min. After treating as usual, *t*-butyl β -hydroxy- β -phenylbutyrate was obtained in a 35% yield.

When acetophenone was replaced by cyclohexanone, the yield of β -hydroxy ester was 26%.

Condensation of Benzophenone and *t*-Butyl Chloroacetate in a Mixture of Benzene and Ether by Means of Magnesium and Mercuric Chloride. — To a mixture of 2.0 g. of magnesium and 0.2 g. of mercuric chloride in 30 ml. of ether was added a few drops of methyl iodide. When the reaction had started, a solution of 9.1 g. of benzophenone and 8.0 g. of *t*-butyl chloroacetate in 40 ml. of benzene was added to obtain the moderate refluxing over a 25-min. period, and refluxing was continued for 90 min. After treating as usual, the recrystallization of the residue from ethanol gave 10.0g. (67%) of *t*-butyl β -hydroxy- β , β -diphenylpropionate, m. p. 92–92.5°. The reported m. p. is 92–92.2°⁶⁾.

Similar condensation of *t*-butyl chloroacetate with cyclohexanone or methyl isobutyl ketone gave the corresponding β -hydroxy ester in yields of 62 and 71% respectively.

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