

## Condensation of Ketones and *t*-Butyl Haloacetates in the Presence of Aluminum or Lithium

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The Reformatsky reaction with *t*-butyl haloacetate could be effected in the presence of lithium or aluminum, but the latter metal proved to be disappointing as a condensing agent.

Condensation of benzophenone with *t*-butyl chloroacetate and bromoacetate in the presence of lithium gave corresponding  $\beta$ -hydroxy esters in yields of 43 and 58%, respectively, and comparable with those of other condensing methods.

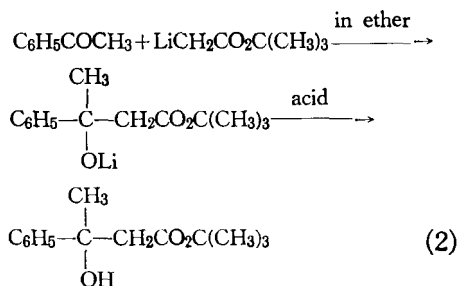
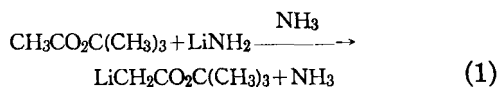
Some workers have already tried various methods to use aluminum instead of zinc as the condensing agent in the Reformatsky reaction. Ray and Dutt<sup>1)</sup>, for example, reported that aluminum powdered, which was activated at 500° in dry hydrogen stream, could be used in the Reformatsky reaction, but its details are now uncertain. Or Arndt et al.<sup>2)</sup> obtained a small amount of  $\gamma$ -chloroacetoacetate by treating chloroacetate with clear aluminum.

Treibs and Mayer<sup>3)</sup> found out that aluminum could be useful in the Reformatsky reaction: Aluminum powder, which was washed with hydrobromic acid, dried, added a small amount of ferric sulfide (1/100—1/50 amount of aluminum) and was treated with iodine vapour, was useful as the condensing agent in the Reformatsky reaction. They obtained ethyl  $\gamma$ -bromoacetoacetate, ethyl acetoacetate and ethyl acetate in yields of 20, 8 and 25%, respectively, by treating ethyl bromoacetate with aluminum in boiling xylene, and obtained ethyl  $\beta$ -hydroxy- $\beta$ -phenylbutyrate in a 24% yield by treating acetophenone and ethyl bromoacetate with activated aluminum. As in the case of ethyl bromoacetate itself, the formation of  $\beta$ -keto ester (i. e. ethyl  $\beta$ -bromoacetoacetate and acetoacetate) by self-condensation, which caused to reduce the yields of  $\beta$ -hydroxy ester in the Reformatsky reaction<sup>4)</sup>, occurred in yields of 33%. From these results, it is expected that the use of *t*-butyl halo esters should increase the yields of  $\beta$ -hydroxy esters<sup>5-8)</sup>.

The present author tried the condensation of *t*-butyl bromoacetate and ketone with powdered aluminum, which was washed with 48% hydrobromic acid, water, acetone, dried and added

mercuric chloride, but the results were disappointing; the condensation of *t*-butyl bromoacetate with acetophenone or with methyl isobutyl ketone was realized in yields of 23 and 28%, respectively, whereas Treibs method was realized in yield of 24% in the former case, and the condensation of *t*-butyl bromoacetate with acetophenone and methyl isobutyl ketone by means of magnesium was realized in 89 and 78% yield, respectively<sup>8)</sup>. Thus, it is concluded that the use of aluminum as condensing agent in the Reformatsky reaction is meaningless in synthetic method by the use of *t*-butyl ester in spite of its advantageous properties<sup>6,8)</sup>.

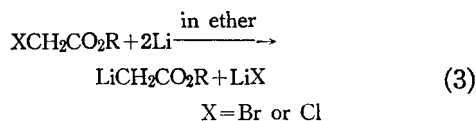
On the other hand, Hauser et al.<sup>9,10)</sup> obtained  $\beta$ -hydroxy ester by condensation of ketone and ester with lithium amide and considered the reaction mechanism as follows:



namely, lithioacetate is formed as intermediate (equation 1) and condensed with the carbonyl group of the ketone to form the  $\beta$ -hydroxy ester (equation 2).

It is well-known that organic halides react with lithium in ether to form the organolithium

compounds<sup>11</sup>); for example, *n*-butyl bromide react with lithium in various solvents to form *n*-butyl lithium<sup>12,13</sup>). Therefore the reaction between lithium and haloacetate is considered to give a lithioacetate (equation 3) and then to occur the same condensation reaction as the Reformatsky reaction by the presence of more reactive carbonyl compounds at the same time. In this case the self-condensation of lithio ester formed is considered to occur but prevented by the use of *t*-butyl group as ester component<sup>5</sup>).



Thus, to a mixture of ether and lithium was added a solution of *t*-butyl haloacetate and a ketone in ether, and the reaction mixture was decomposed with dilute acidic solution after refluxing was continued for about 2 hr. The experimental results are summarized in Table I along with the results made by using aluminum.

Table I  
The Condensation of *t*-Butyl Haloacetate with Ketone in the Presence of Aluminum or Lithium

Ester <i>t</i> -Butyl	Condensing Agent	Ketone	Yield(%) of <i>t</i> -Butyl $\beta$ -Hydroxy Ester
Bromoacetate	Aluminum	Acetophenone	23
Bromoacetate	Aluminum	Methyl Isobutyl Ketone	28
Bromoacetate	Lithium	Acetophenone	29
Bromoacetate	Lithium	Benzophenone	58
Chloroacetate	Lithium	Benzophenone	43

These results are inferior to those reported for the usual Reformatsky reaction and aldol-type condensation employed for the preparation of  $\beta$ -hydroxy ester. Meanwhile, condensation of *t*-butyl chloroacetate with benzophenone was realized in yield of 43%, whereas the corresponding Reformatsky reaction using ethyl chloroacetate has been reported to produce in yield of 30%<sup>14</sup>), then it is concluded that the use of lithium instead of zinc or magnesium in the Reformatsky reaction was realized with some superior yield in some case.

#### Experimental \*

**Aluminum powder** used was treated with 48% hydrobromic acid and was washed with water and with acetone, and dried in a dryer.

**Condensation of Acetophenone and *t*-Butyl Bromoacetate with Aluminum.**— In a 100 ml. flask were placed 5.0g. of powdered aluminum, 0.5g. of mercuric chloride and 60ml. of anhydrous xylene (distilled with sodium) and distilled off 20 ml. of xylene to result reddish mixture. When a temperature of content showed 80°, a mixture of 6.0g. of acetophenone and 10.0g. of *t*-butyl bromoacetate<sup>8</sup>) was added with stirring to obtain the moderate refluxing over a 20-min. period. After the mixture was reflux-

ed for 30 min., 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 under diminished pressure. The residue was distilled, and *t*-butyl  $\beta$ -hydroxy- $\beta$ -phenylbutyrate (2.7g., 23% yield) was obtained as a pale-yellow oil, b. p. 135–140°/7–8 mm. Reported b. p. is 111–112.5°/2 mm.<sup>9</sup>) and 125–126°/6 mm.<sup>8</sup>).

When acetophenone was replaced by methyl isobutyl ketone, the yield of *t*-butyl  $\beta$ -hydroxy- $\beta$ -isobutylbutyrate, b. p. 100°/10 mm., was 28%. Reported b. p. is 114–115°/8 mm.<sup>9</sup>) and 99–100°/10 m.<sup>15</sup>).

**Condensation of Benzophenone and *t*-Butyl Bromoacetate with Lithium.**— To a mixture of 0.38 g. of lithium and 30 ml. of anhydrous ether was added a few drops of ethyl bromide. When the reaction had started, a solution of 4.5g. of benzophenone and 5.0g. of *t*-butyl bromoacetate in 20 ml. of ether was added with stirring at a rate designed to maintain gentle refluxing. After stirring and refluxing for 140 min., the reaction mixture was cooled and decomposed with a cold 10% sulfuric acid. The organic layer was separated and aqueous

\*) All boiling and melting points are uncorrected.

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. Recrystallization of the residue from ethanol gave 4.8 g. (58%) of *t*-butyl  $\beta$ -hydroxy- $\beta$ ,  $\beta$ -diphenylpropionate, m. p. 92—92.5°. Reported m. p. is 92—92.2°<sup>8)</sup> and 92—93°<sup>15)</sup>.

When benzophenone was replaced by acetophenone, the yield of  $\beta$ -hydroxy ester was 29%.

Similar condensation of *t*-butyl chloroacetate<sup>15)</sup> with benzophenone gave the corresponding  $\beta$ -hydroxy ester in yield of 43%.

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