Claisen Condensation by *t*-Butylmagnesium Chloride

BY H. D. ZOOK, W. J. MCALEER AND LEVONNA HORWIN

t-Butylmagnesium chloride reacts with esters of higher molecular weight acids to give 35–45% yields of symmetrical ketones. This reaction was first described by Petrov[1] as a new abnormal Grignard reaction occurring by the following scheme.

$$2RCOOC_2H_5 \longrightarrow RCOR + CO_2 + (C_2H_5)_2O$$

We have found that the ketones are not the initial products of the reaction but result from the hydrolysis of β-ketoesters formed by a Claisen type condensation of the ester by the basic Grignard reagent.

$$2RCH_2CO_2C_2H_5 \xrightarrow{(CH_3)_3CMgCl} RCH_2COCHRCO_2C_2H_5 \xrightarrow{H_2O} (RCH_2)_2CO$$

i-Propylmagnesium bromide and mesitylmagnesium bromide previously have been shown to effect Claisen condensations of certain esters.[2]

That the β-ketoester is the intermediate product is shown by the complete solubility of the reaction product in a small amount of ether. Mild hydrolysis gives a copious precipitation of the symmetrical ketone which is only sparingly soluble in ether. With lower esters the β-keto ester can be isolated by fractional distillation. Thus, *t*-butylmagnesium chloride and ethyl propionate give a 50% yield of ethyl propionylpropionate.

Contrary to Petrov,[3] it was found that the reaction of the Grignard reagent with the ester does not require temperatures of 110–120° but proceeds smoothly at room temperature with the evolution of isobutane and isobutene.

The symmetrical ketone is not the exclusive product of the reaction as claimed.[1] Yields from eight runs of *t*-butylmagnesium chloride on the methyl and ethyl esters of myristic and palmitic acids were all below 50%. Normal addition of the Grignard reagent to the ester to give the expected ketone, RCOR′, followed by reduction of this ketone to the secondary alcohol also occurs as a simultaneous reaction.[4] High vacuum distillation of the mother liquors from the crystallization of myristone in one experiment gave a 40% of *t*-butyltridecylcarbinol.

Experimental

Grignard reagents were prepared at 15° from carefully fractionated *t*-butyl chloride in dry ether. The solutions were forced with nitrogen through fine glass wool filters and titrated in the usual manner.

Condensation of Methyl Myristate.—The usual apparatus for the Grignard reaction and an atmosphere of nitrogen were employed. A solution of 490 cc. (1.08 moles) of *t*-butylmagnesium chloride was added with stirring over a period of seven hours to 77 g. (0.32 mole) of the ester in 200 cc. of dry ether. Heat and gas were evolved at once. The flask was cooled in a water-bath to prevent refluxing. Stirring was continued overnight and finally the water bath heated to 40° to drive out the remainder of the gases. The total gases from the reaction were shown by distillation and absorption methods to consist of 0.09 mole of isobutene and 0.17 mole of isobutane. The reaction mixture was hydrolyzed with excess dilute hydrochloric acid and the organic layer concentrated to an oil by removal of most of the ether. Cooling the ether solution at several concentrations failed to give a precipitate.

The oil was dissolved in 400 cc. of ethanol and refluxed overnight with 200 cc. of 10% sodium hydroxide. Most of the ethanol was removed under vacuum and the residue diluted with 500 cc. of water and extracted with 500 cc. of ether. Much white solid was present at the interface. The ether layer and solid were washed well with water and filtered to give 22 g. (35%) of myristone, melting point and mixed melting point with an authentic sample 77–78°; oxime, m. p. and mixed m. p. 50–51°. Concentration of the mother liquor gave a 5.5 g. (9%) second crop, m. p. 75–77°. Further concentration gave 44 g. of oil which would not solidify at 0°. Acidification of the alkaline layer gave 6 g. (8%) of myristic acid, m. p. 53–55° after one crystallization from ethanol.

High vacuum distillation of the non-crystallizable oil gave six fractions totaling 37 g. (40%) of *t*-butyltridecylcarbinol, b. p. 87–90° at 10^{-4} mm., $n^{20}D$ 1.4490–1.4491, m. p. 12–14°. The alcohol was dehydrated by passing the vapors at 1 mm. through a 1.7 × 50 cm. column packed with alumina and heated to 280–300°. The olefin distilled at 60–67° at 10^{-4} mm., $n^{20}D$ 1.4465–1.4478. Titration with bromine by the Francis method[5] gave a mol. wt. of 255 (calcd. for $C_{18}H_{36}$: mol. wt., 252). Oxidation of 16.5 g. of the olefin by the procedure of Armstrong and Hilditch[6] using 40 g. of potassium permanganate in saturated acetone solution gave 1.5 g. (21%) of trimethylacetic acid, b. p. 95–98° at 60 mm., 155–160° at 740 mm.; neutral equivalent, 105; calcd. for $C_5H_{10}O_2$, 104; anilide, m. p. and mixed m. p. 129–130°; S-benzylthiouronium salt, m. p. and mixed m. p. 145–146°. Also obtained was 4.9 g. (35%) of *n*-tridecanoic acid, b. p. 118° at 0.5 mm., m. p. 38–40°[7]; neutral equivalent, 211; calcd. for $C_{13}H_{26}O_2$, 214; *p*-phenylphenacyl ester, m. p. 84–85°.[8]

Condensation of Ethyl Propionate.—To 102 g. (1 mole) of the ester dissolved in 100 cc. of dry ether was added 770 cc. (1.7 moles) of *t*-butylmagnesium chloride solution. The mixture was cooled in a water bath to prevent refluxing, stirred until solid and allowed to stand for five days. Hydrolysis with excess dilute hydrochloric acid and careful fractionation of the organic layer through a 10-plate column gave 23 g. (20%) of ethyl-*t*-butylcarbinol, b. p. 44–45° at 15 mm., $n^{20}D$ 1.4215–1.4218; α-naphthylurethan, m. p. 109–110°[9] and 39 g. (50%) ethyl propionylpropionate, b. p. 62–63° at 5 mm., $n^{20}D$ 1.4230–1.4232. The ketoester gave a deep blue color with dilute ferric chloride solution. Identification was made by hydrolysis of 5 g. of the ketoester by warming one hour on the steam-bath with 60 cc. of 5% potassium hydroxide solution. Obtained was 1.7 g. of diethyl ketone, b. p. 101° at 740 mm.; 2,4-dinitrophenylhydrazone, m. p. 154–155°; mixed m. p. with an authentic sample 155–156°.

DEPARTMENT OF CHEMISTRY
PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PA.

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[1] A. D. Petrov, *Sci. Records Gorky State Univ.*, **7**, 3 (1939); *C. A.*, **35**, 435 (1941).

[2] Conant and Blatt, THIS JOURNAL, **51**, 1227 (1929); Spielman and Schmidt, *ibid.*, **59**, 2009 (1937); Hauser and Hudson's chapter in "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 277.

[3] Petrov, Karasev and Cheltzova, *Bull. soc. chim.*, [5] **3**, 169 (1936).

[4] *Cf.* Whitmore and Forster, THIS JOURNAL, **64**, 2966 (1942).

[5] Francis, *Ind. Eng. Chem.*, **18**, 821 (1926).

[6] Armstrong and Hilditch, *J. Soc. Chem. Ind.*, **44**, 43T (1925).

[7] Pool and Ralston, *Ind. Eng. Chem.*, **34**, 1104 (1942).

[8] Price and Griffith, THIS JOURNAL, **62**, 2884 (1940).

[9] Whitmore, Meyer, Pedlow and Popkin, *ibid.*, **60**, 2788 (1938).