Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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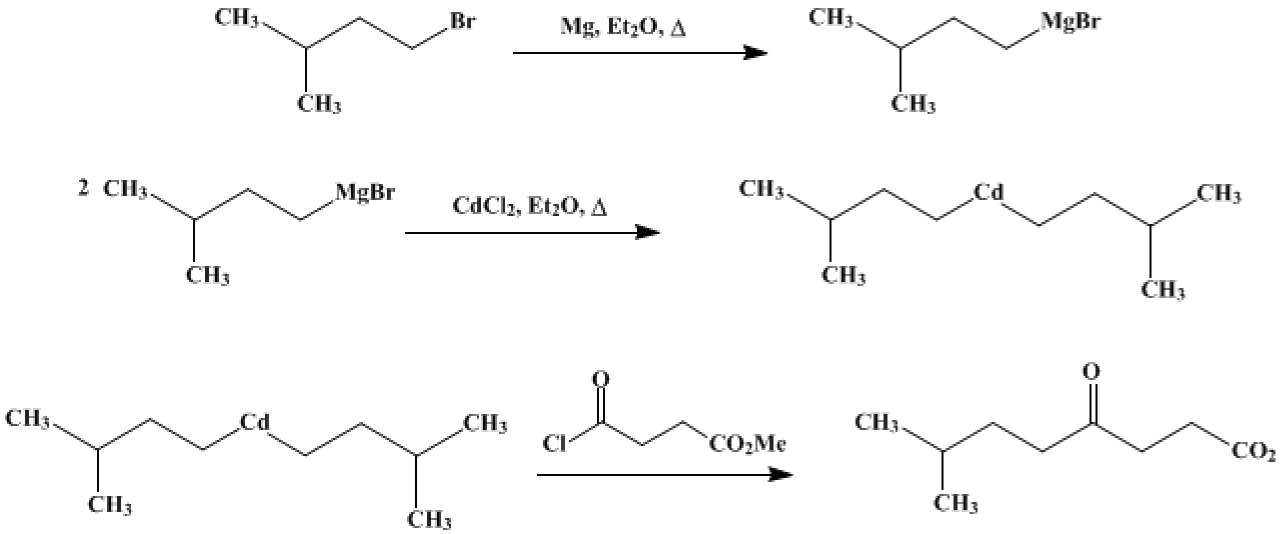
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 3, p.601 (1955); Vol. 28, p.75 (1948).

METHYL 4-KETO-7-METHYLOCTANOATE

[Caprylic acid, ζ-methyl-γ-oxo-, methyl ester]



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1. Procedure

A 2-l. three-necked flask (Note 1) is fitted with a reflux condenser having a take-off attachment,[1] a mercury-sealed Hershberg stirrer (Note 2), and a 500-ml. dropping funnel (Note 1). A nitrogen inlet tube is connected to the top of the condenser, and a branch of the tube, connected by means of a T-tube, is connected to a mercury valve[1] consisting of a U-tube, the bend of which is just filled with mercury. Unless the dropping funnel is equipped with a pressure-equalizing side tube,[1] a second branch of the nitrogen line is arranged for connection to its mouth. In the flask is placed 24.3 g. (1.0 gram atom) of magnesium turnings, and the entire flask is warmed with a soft flame while a slow stream of nitrogen is passed through and permitted to escape by way of the dropping funnel. The flask is allowed to cool, the dropping funnel is closed, and the nitrogen flow is reduced until the gas bubbles very slowly through the mercury valve. The magnesium is covered with 150 ml. of dry ether, introduced from the dropping funnel, and a solution of 151 g. (1.0 mole) of pure isoamyl bromide (Note 3) in 350 ml. of dry ether is placed in the dropping funnel. A few milliliters of the bromide solution is added to the flask, and the stirrer is started. The flask is warmed gently if the reaction does not start spontaneously. The remainder of the bromide is added during 1–2 hours, and the mixture is refluxed for 15 minutes longer. The flask is then cooled in an ice bath, the dropping funnel is removed, and 98 g. (0.535 mole) of anhydrous C.P. cadmium chloride (Note 4) is added over a period of 5–10 minutes. After all the cadmium chloride has been added, the ice bath is removed and the mixture is stirred for 5 minutes and then heated under reflux with stirring for an additional 45 minutes (Note 5).

Ether is now rapidly distilled from the reaction mixture (Note 6) by heating on a steam bath. Distillation is continued with stirring until it becomes very slow and a dark viscous residue remains. The distillate amounts to 250–325 ml. At this point, 350 ml. of dry thiophene-free benzene is added to the flask and the distillation is continued until an additional 100 ml. of distillate has been collected. A second 350-ml. portion of dry benzene is added to the flask, and the mixture is refluxed with vigorous stirring for a few minutes in order to break up the cake in the flask and disperse it through the mixture. The heating bath is then removed, and 120 g. (0.8 mole) (Note 7) of β-carbomethoxypropionyl chloride (p. 169) in 150 ml. of dry benzene is added from the dropping funnel. This addition, which causes vigorous refluxing, requires 10–20 minutes. During this time the heavy precipitate changes in appearance and stirring becomes more difficult. After the addition of the acid chloride is complete and spontaneous refluxing has stopped, the mixture is stirred and heated under reflux for an additional hour.

The reaction mixture is cooled in an ice bath and decomposed in the usual way by the careful addition of about 600 g. of ice and water, followed by sufficient 20% sulfuric acid to give two clear phases (Note 2). The aqueous phase is separated in a 2-l. separatory funnel and extracted with two 100-ml. portions of benzene. The two benzene extracts are placed in two 500-ml. separatory funnels. The original benzene layer and each extract are washed successively (Note 8) with 200 ml. of water, 200 ml. of 5% sodium carbonate solution, 200 ml. of water, and 100 ml. of saturated sodium chloride solution, and then each is filtered through a layer of anhydrous sodium sulfate. A little fresh solvent is used to rinse the separatory funnels and the filter.

A fractionating column (Note 9) is connected to a 250-ml. flask carrying a dropping funnel and heated in an oil bath at 150–160°. The combined benzene solutions are run into the flask from the dropping funnel so that the benzene is removed by flask distillation at atmospheric pressure. The pressure is then lowered, and after the distillation of the last of the solvent and a little 2,7-dimethyloctane (from coupling of the Grignard reagent) the vapor temperature rises to about 100°/20 mm. About 5 g. of methyl ethyl succinate (Note 10) and (Note 11) is collected at 100–106°/20 mm., and after an intermediate fraction (about 3 g.) the keto ester is collected at 136–137°/20 mm. (Note 11) and (Note 12). The yield of methyl 4-keto-7-methyloctanoate is 108.5–111.5 g. (73–75%, based on β-carbomethoxypropionyl chloride) (Note 13) and (Note 14).

2. Notes

1. Connections may be made with rubber stoppers, but ground-glass joints are preferable.
2. The heavy sludges encountered in this preparation make a strong and efficient stirrer essential. A stirrer of the Hershberg type of tantalum wire is preferable, but new, unetched Nichrome is quite satisfactory. If a Nichrome stirrer is used it should be removed before acid is added to complete the decomposition of the organometallic complex.
3. Isoamyl bromide, b.p. 120–120.5°, was prepared as previously described.[2] The product was fractionated through a packed column, such as that referred to in (Note 9) below, to remove small quantities of *tert*-amyl bromide arising from *sec*-butyl carbinol present in the isoamyl alcohol.
4. The cadmium chloride is dried to constant weight at 110° in an oven, ground thoroughly, and stored in a desiccator. If stored in a screw-cap bottle in the laboratory it may absorb moisture slowly.
5. It is best to continue stirring at this point until the mixture gives a negative Gilman test for the Grignard reagent.[3] One-half milliliter of the reaction mixture is added to an equal volume of a 1% solution of Michler's ketone in dry benzene. After this mixture is shaken briefly, 1 ml. of water is added, followed by a few drops of a 0.2% solution of iodine in glacial acetic acid and 0.5 ml. of glacial acetic acid. If any Grignard reagent is still present, a greenish blue color is observed.
6. If the reaction with the acid chloride is carried out in ether solution larger amounts of methyl ethyl succinate are formed, and the yield of keto ester is only 42–59%.
7. The use of β-carbomethoxypropionyl chloride of poor quality frequently resulted in poor yields of the desired keto ester. It is most important that the methyl hydrogen succinate, m.p. 56–57°, from which the acyl chloride is prepared, be of high quality and that it be ground thoroughly before drying. The melting point of a sample of methyl hydrogen succinate is not a sufficient criterion of purity, so that the neutral equivalent of the sample of ester should be determined. If the neutral equivalent is not in the range 130–134, the reagent should be purified by recrystallization.
8. The indicated portion of each wash solution is used to wash each of the benzene solutions in turn. If three separatory funnels are used this process is not laborious and results in very thorough extraction.
9. An efficient column packed with glass helices and provided with a heating jacket and a suitable head[4] should be used. Columns of dimensions 50 cm. by 14 mm. i.d. and 43 cm. by 12 mm. i.d. have been found satisfactory.
10. The methyl ethyl succinate apparently results from the reaction of the acid chloride with ether.
11. The apparent boiling points of the fractions may vary somewhat, depending on the fractionating column.
12. Boiling points of the keto ester at other pressures are as follows: 117°/8 mm., 120–122°/11 mm.,

125°/14 mm., 139.5°/22 mm., and 145°/27 mm.

13. In an alternative procedure the fractionating column is removed after the intermediate fraction has been collected, and the residual ester is distilled through a short still head.

14. The procedure described has been used by the submitters for the preparation of the following keto esters:

Keto Ester	*B.P.*	*% Yield*
Ethyl 10-keto-13-methyltetradecanoate	180–182°/3 mm.	85
Ethyl 10-keto-16-methyloctadecanoate	192–195°/2 mm.	76.5
Ethyl 6-ketoheptanoate	143–145°/33 mm.	76
Ethyl 10-ketohendecanoate	137–138°/2 mm.	83
Ethyl 10-keto-14-methyltetracosanoate	242–245°/1 mm.	77

The ester acid chlorides used in these preparations, ω-carbethoxyvaleryl chloride and ω-carbethoxynonanoyl chloride, were obtained from the corresponding half esters in yields of 90–95%. The method described for β-naphthoyl chloride (p.629, Note 2) was used, but since with these acids the reaction is much more vigorous the phosphorus pentachloride was added in small portions and the mixture was not heated until after the exothermic reaction had subsided.

The procedure described failed completely when a secondary bromide, 2-bromopentane, was used; however, when the cadmium derivative was prepared at −5° to −7° and allowed to react in ether at this temperature with β-carbomethoxypropionyl chloride, methyl 4-keto-5-methyloctanoate was obtained in a yield of 19.3%, b.p. 130.5–130.7°/21 mm.

3. Discussion

Methyl 4-keto-7-methyloctanoate has been prepared by the procedure given, which is based on the method of Cason and Prout.[5] The use of cadmium derivatives for the preparation of simple ketones was introduced by Gilman and Nelson.[6]

A preparation from isobutyl-2-furylcarbinol (obtained by a Grignard reaction from furfural) has also been described.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 93
- Org. Syn. Coll. Vol. 5, 813

References and Notes

1. Fieser, *Experiments in Organic Chemistry*, 2nd Ed., p. 323, Fig. 49; p. 404, Fig. 75, D. C. Heath and Company, Boston, 1941.
2. *Org. Syntheses* Coll. Vol. **1**, 27 (1941).
3. Gilman and Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925); Gilman and Heck, *J. Am. Chem. Soc.*, **52**, 4949 (1930).
4. Whitmore and Lux, *J. Am. Chem. Soc.*, **54**, 3448 (1932).
5. Cason and Prout, *J. Am. Chem. Soc.*, **66**, 46 (1944); Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946); *Chem. Revs.*, **40**, 15 (1947).
6. Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).
7. Kucherov, *Zhur. Obshcheii Khim.*, **20**, 1885 (1950) [*C. A.*, **45**, 2928 (1951)].

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Caprylic acid, ζ-methyl-γ-oxo-, methyl ester

acyl chloride

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

magnesium,
magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

bromide (24959-67-9)

sodium carbonate (497-19-8)

Isoamyl bromide (107-82-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury (7439-97-6)

iodine (7553-56-2)

Furfural (98-01-1)

isoamyl alcohol (123-51-3)

2-bromopentane (107-81-3)

β-Carbomethoxypropionyl chloride (1490-25-1)

Methyl hydrogen succinate (3878-55-5)

Methyl 4-keto-7-methyloctanoate (53663-32-4)

cadmium chloride (10108-64-2)

2,7-dimethyloctane (1072-16-8)

methyl ethyl succinate

Ethyl 10-keto-13-methyltetradecanoate

Ethyl 10-keto-16-methyloctadecanoate

Ethyl 6-ketoheptanoate

Ethyl 10-ketohendecanoate

Ethyl 10-keto-14-methyltetracosanoate

ω-carbethoxyvaleryl chloride

ω-carbethoxynonanoyl chloride

β-naphthoyl chloride (2243-83-6)

isobutyl-2-furylcarbinol

tert-amyl bromide (507-36-8)

sec-butyl carbinol (137-32-6)

methyl 4-keto-5-methyloctanoate