Organic Syntheses

A Publication
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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.

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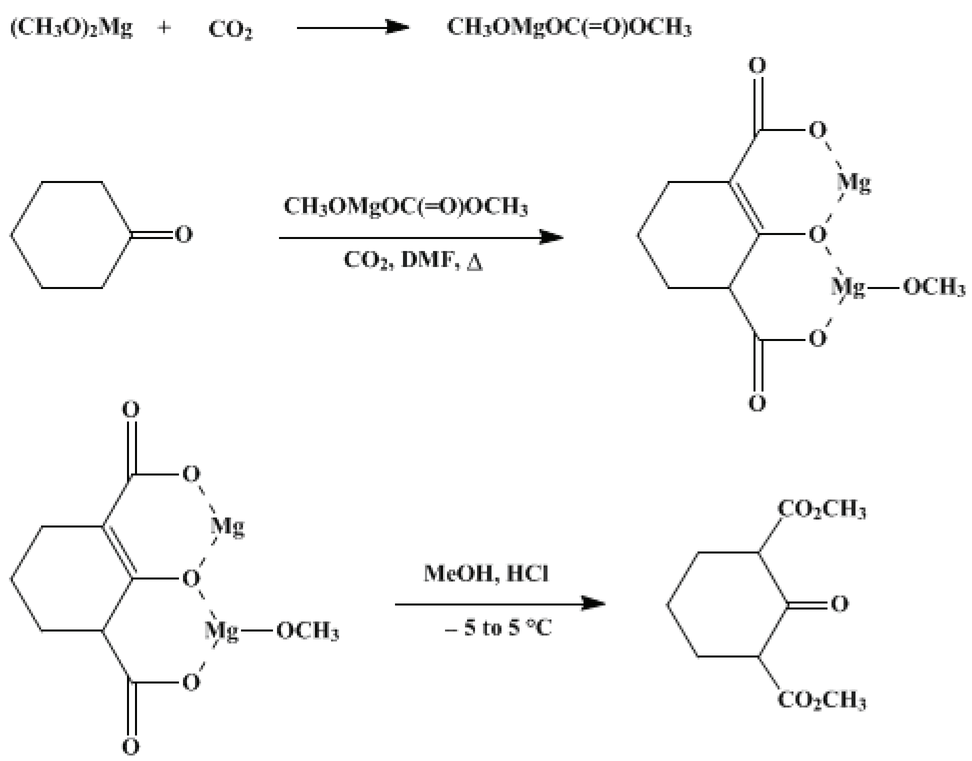
DIMETHYL CYCLOHEXANONE-2,6-DICARBOXYLATE

[Cyclohexanone-2,6-dicarboxylic acid, dimethyl ester]



Submitted by S. N. Balasubrahmanyam and M. Balasubramanian[1].
Checked by Frederick J. Sauter and Herbert O. House.

1. Procedure

Caution! Since hydrogen is liberated in the first step of this reaction, it should be conducted in a hood. A dry 2-l. three-necked flask is fitted with a Trubore mechanical stirrer, an Allihn condenser, and a 1-l. pressure-equalizing dropping funnel, the top of which is fitted with a gas inlet tube. After 40.0 g. (1.64 g. atoms) of clean, dry magnesium ribbon (Note 1) has been placed in the flask, the system is flushed with nitrogen and 600 ml. of anhydrous methanol (Note 2) is added. As soon as the vigorous reaction begins, the nitrogen flow is stopped; if necessary, the reaction may be moderated by external cooling with wet towels. When the hydrogen evolution has ceased, a slow stream of nitrogen is passed through the reaction system and the condenser is replaced by a total condensation-partial take-off distillation head. The nitrogen flow is stopped, and the bulk of the methanol is distilled from the solution under reduced pressure (Note 3) with stirring while the reaction flask is heated to 50–55° with a water bath. This distillation is stopped when stirring of the pasty suspension of magnesium methoxide is no longer practical. Nitrogen is readmitted to the system, and the outlet from the distillation head is attached to a small trap containing mineral oil so that the volume of gas escaping from the reaction system can be estimated. Anhydrous dimethylformamide (700 ml.; (Note 4)) is added to the reaction flask, and the resulting suspension is stirred vigorously while a stream of anhydrous carbon dioxide (Note 5) is passed into the reaction vessel through the gas inlet tube attached to the dropping funnel. The dissolution of the carbon dioxide is accompanied by an exothermic reaction with the suspended magnesium methoxide to form a solution. When the absorption of carbon dioxide has stopped (Note 6), the colorless solution is heated with a mantle under a slow stream of anhydrous carbon dioxide gas until the temperature of the liquid distilling from the flask reaches 140°, indicating that the residual methanol has been removed from the reaction mixture. The flow of carbon dioxide is stopped, and a slow stream of nitrogen is passed through the system while the resulting solution (Note 7) is cooled below 100° with a water bath. Cyclohexanone (20.0 g., 0.204 mole) (Note 8) is added to the reaction mixture, and the solution is heated under reflux for 2 hours while a slow stream of nitrogen (2–3 bubbles per second) is passed over the reaction mixture. The resulting solution is cooled first to room temperature with a water bath and then to −5° with a dry ice-acetone bath (Note 9).

Meanwhile, 700 ml. of anhydrous methanol is placed in a 2-l. flask fitted with a gas inlet tube extending approximately 5 mm. below the surface of the methanol and a calcium chloride tube to protect the contents of the flask from atmospheric moisture. The methanol is cooled with an external cooling bath prepared from ice and calcium chloride (Note 10) and saturated with anhydrous hydrogen chloride (Note 10) (290–300 g. of hydrogen chloride is required). This solution is transferred to the dropping funnel by means of a gooseneck adapter and the methanolic hydrogen chloride solution is then added, dropwise and with stirring, to the reaction flask, the temperature of the reaction being maintained at 0° ± 5° by means of a cooling bath. This addition is accompanied by the vigorous evolution of carbon dioxide and the separation of a white solid. After the addition is complete, the reaction mixture is allowed to stand overnight at room temperature and then the bulk of the methanol is removed from the solution by distillation under reduced pressure with stirring. During the distillation the temperature of the reaction mixture is kept below 55°. The remaining suspension is poured into a 4-l. beaker containing 1 kg. of crushed ice. The crude product separates as shiny white flakes which are collected on a filter and washed with water. A small second crop of the crude material may be obtained by cooling the aqueous filtrates to 0° overnight. The total crude product (25–26 g.) is dissolved in 250 ml. of boiling methanol, and this solution is concentrated to 125–150 ml. and allowed to cool. The keto diester separates as flat white needles, m.p. 128–132° (Note 11), yield 19.3–19.7 g. (44–45%). Concentration of the mother liquors affords an additional 2.2– 2.5 g. of crude product, m.p. 122–128° (Note 11).

2. Notes

1. Magnesium ribbon is conveniently cleaned by immersion in aqueous 10% hydrochloric acid, rinsing the ribbon with distilled water and with acetone, and drying it in an oven at 120°.
2. To ensure a rapid reaction with the magnesium, the methanol should be heated to reflux over magnesium methoxide for 12 hours and then distilled and transferred to the reaction vessel with a siphon or a large pipet. If necessary, a crystal of iodine may be added to initiate the reaction of methanol with magnesium.
3. If a water aspirator is used, a calcium chloride tube or tower should be included in the line connecting the distillation head and the aspirator.
4. The dimethylformamide may be purified by distillation at atmospheric pressure. The checkers distilled material purchased from the J. T. Baker Company and used the fraction collected at 153–155°.
5. Carbon dioxide obtained from a cylinder of the compressed gas was passed through a tube packed with calcium chloride and either activated silica gel or Drierite (containing an indicator) to remove water.
6. If the gas flow is turned off while carbon dioxide is still being absorbed, the pressure inside the flask falls below atmospheric pressure. This pressure change is readily observed with the mineral oil-filled trap fitted to the gas exit tube of the system.
7. The submitters found that this solution of methyl magnesium carbonate in dimethylformamide could be stored for long periods in a well-stoppered bottle without loss of potency.
8. The checkers employed cyclohexanone purchased from Eastman Organic Chemicals and distilled before use, b.p. 155–157°. The ratio of cyclohexanone to methylmagnesium carbonate is fairly critical; a proportion of ketone larger than the ratio 1:8 ketone:magnesium salt specified yields a pasty product presumably contaminated with monocarboxylated material. A smaller proportion of ketone lowers the yield.
9. The checkers measured the temperature of this solution by sliding a thermometer through the distillation head so that the thermometer bulb was immersed in the reaction mixture.
10. The checkers used a cooling bath prepared from ice and sodium chloride and dried the hydrogen chloride obtained from a compressed-gas cylinder by passing the gas through a trap filled with concentrated sulfuric acid.
11. The submitters reported that the addition of eight volumes of warm (35°) water to a warm solution of the keto diester in ten volumes of methanol followed by gradual cooling to 0° separated, on one

occasion, a product, m.p. 142–143°, which was presumably one pure isomer. The checkers found that the product recrystallized readily from methanol, aqueous methanol, or benzene in good crystalline form but invariably with a wide melting range (129–136°) which varied with the rate of heating. It would appear that the checkers invariably obtained the product as a mixture of two or more of the three readily interconvertible forms: keto *cis*-diester, keto *trans*-diester, and enol diester. The thin-layer chromatogram of the recrystallized product, determined on a plate coated with silica gel and eluted with a mixture of carbon tetrachloride and ethyl acetate (1:1 v/v), indicated the absence of monocarbomethoxycyclohexanone in the product. Also, the elemental composition of the product and the mass spectrum of the product are consistent with the idea that the product contains only stereoisomeric and tautomeric forms. The mass spectrum exhibits a molecular ion peak at *m/e* 214 with abundant fragment peaks at *m/e* 182, 154, 126, 95, 67, and 55 but exhibits a peak of relatively low abundance at *m/e* 156, the mass of the molecular ion derived from 2-carbomethoxycyclohexanone. An ethanol solution of the recrystallized keto diester product initially exhibits an ultraviolet maximum at 255 mμ with a molecular extinction coefficient within the range 6000–11,000; on the addition of excess sodium hydroxide the ultraviolet maximum is shifted to 287.5 mμ (ε 12,600). A chloroform solution of the recrystallized product has infrared absorption at 1750 (strong), 1712 (medium), 1675 (weak), and 1610 (weak) cm.$^{-1}$; an ethanol solution of the product, when treated with ferric chloride, gives no immediate color, but a brown color develops after the solution is allowed to stand for 10 to 20 minutes. These observations suggest that the crystalline product obtained in this preparation is primarily a mixture of the *cis*- and *trans*-isomers of the keto tautomer.

3. Discussion

Dimethyl cyclohexanone-2, 6-dicarboxylate has been prepared by the alkylation of dimethyl acetonedicarboxylate with trimethylene dibromide[2] and by the carboxylation of cyclohexanone.[3] The present preparation gives a general procedure for carboxylation of active methylene compounds.[3,4,5,6] The method has been used for carboxylation of methylene groups activated by ketones,[3,4,5] nitro groups,[3,4] and certain amide functions.[6] The success of the procedure is attributed to the formation of a magnesium enolate which is stabilized by chelation with an adjacent carboxylate anion.[4,6] In certain cases[3,6] the magnesium enolate has been alkylated in the original reaction mixture, thereby avoiding the necessity for isolating an intermediate ester. Although the present example illustrates the fact that when two equivalent active methylene groups are present both positions may be carboxylated, the submitters were unsuccessful in obtaining a pure keto diester when the procedure was applied to cyclopentanone.

References and Notes

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

Drierite

activated silica gel

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride,
hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

magnesium,
magnesium ribbon (7439-95-4)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

trimethylene dibromide (109-64-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

iodine (7553-56-2)

acetone (67-64-1)

ferric chloride (7705-08-0)

Cyclopentanone (120-92-3)

magnesium methoxide

methylene (2465-56-7)

dimethylformamide (68-12-2)

Dimethyl cyclohexanone-2,6-dicarboxylate,
Cyclohexanone-2,6-dicarboxylic acid, dimethyl ester,
Dimethyl cyclohexanone-2, 6-dicarboxylate (25928-05-6)

methyl magnesium carbonate

methylmagnesium carbonate

monocarbomethoxycyclohexanone,
2-carbomethoxycyclohexanone (41302-34-5)

dimethyl acetonedicarboxylate