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.

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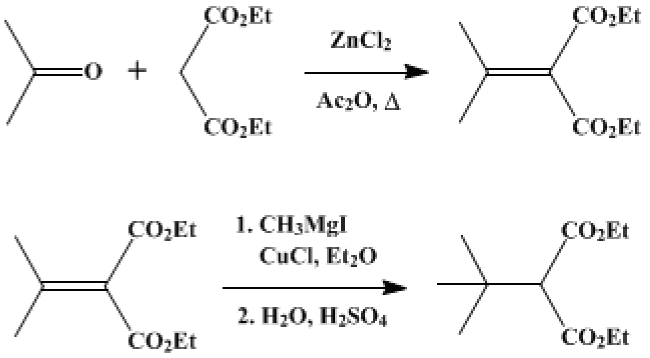
DIETHYL *tert*-BUTYLMALONATE

[Propanedioic acid, (1,1-dimethylethyl)-, diethyl ester]



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1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[4] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A. *Diethyl isopropylidenemalonate*. A 2-l. flask equipped with a magnetic stirrer and a reflux condenser fitted with a calcium chloride drying tube is charged with 400 g. (2.50 moles) of diethyl malonate (Note 1), 216 g. (3.73 moles) of acetone (Note 2), 320 g. (3.14 moles) of acetic anhydride, and 50 g. (0.37 mole) of anhydrous zinc chloride (assay 98.9%, (Note 3)). The solution is heated at reflux, with stirring, for 20–24 hours, then cooled and diluted with 300–350 ml. of benzene. The resulting dark-colored solution is washed with four 500-ml. portions of water, and the combined aqueous layers are extracted with two 100-ml. portions of benzene. The combined benzene solutions are concentrated with a rotary evaporator, and the residual liquid is fractionally distilled under reduced pressure through a 30-cm. Vigreux column or spinning band column. After separation of the unchanged diethyl malonate [119–135 g., b.p. 85–87° (9 mm.)] and intermediate fractions [b.p. 87–104° (9 mm.)], diethyl isopropylidenemalonate is collected as 231–246 g. (46–49%) of colorless liquid, b.p. 110–115° (9–10 mm.), n_D^{20} 1.4483–1.4490 (Note 4).

B. *Diethyl* tert-*butylmalonate*. A 1-l., three-necked flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, a reflux condenser, and a nitrogen inlet tube is dried in an oven at 110–120°, then flushed with nitrogen and allowed to cool; an atmosphere of nitrogen is maintained in the reaction vessel throughout the subsequently described reactions. After 18.3 g. (0.753 g.-atom) of magnesium turnings have been placed in the flask, a solution of 113.5 g. (0.7993 mole) of methyl iodide (Note 5) in 200 ml. of anhydrous diethyl ether (Note 6) is added dropwise with stirring. The resulting solution of methylmagnesium iodide is cooled to 0–5° with an external ice–salt bath, and 1.0 g. (0.010

mole) of copper(I) chloride is introduced with stirring (Note 7). The temperature of the resulting mixture is kept at −5° to 0° while a solution of 100 g. (0.500 mole) of diethyl isopropylidenemalonate in 100 ml. of anhydrous ether (Note 6) is added, dropwise and with stirring over a period of 80–90 minutes. After the addition is complete, the cooling bath is removed; the reaction mixture is stirred for 30 minutes and poured onto a mixture of 500–1000 g. of ice and 400 ml. of 10% sulfuric acid. The ether layer is separated and the aqueous phase is extracted with three 200-ml. portions of ether. The combined ether solutions are washed with 100 ml. of saturated aqueous sodium thiosulfate (Note 8), dried over magnesium sulfate, and concentrated with a rotary evaporator. The residual liquid is distilled through a short Vigreux column, yielding 93.5–102 g. (87–94%) of diethyl *tert*-butylmalonate as a colorless liquid, b.p. 60–61° (0.7 mm.), n_D^{20} 1.4250 (Note 9).

2. Notes

1. A commercial grade of diethyl malonate was distilled before use, b.p. 90° (15 mm.).
2. The submitters used commercial acetone which was dried over potassium carbonate before use. The checkers dried acetone over Linde Molecular Sieves, No. 4A.
3. The checkers used a proportionate amount (52 g.) of anhydrous zinc chloride (assay, 95% minimum) purchased from the Mallinckrodt Chemical Works.
4. This procedure was described by Cope and Hancock.[5] The product has IR absorption (CCl_4) at 1730 (conjugated ester C=O) and 1650 cm.$^{-1}$ (conjugated C=C) with ^1H NMR peaks (CCl_4) at δ 1.12 (t, J = 7 Hz., 6H), 2.01 (s, 6H), 4.10 (q, J = 7 Hz., 4H), and a UV maximum (95% EtOH) at 218 nm (ε 10,200).
5. Reagent grade methyl iodide, obtained from J. T. Baker Chemical Company, Philadelphia, was used without further purification. The checkers used a pure grade of methyl iodide purchased from Eastman Organic Chemicals without further purification.
6. Anhydrous ether, from freshly opened containers, obtained from the Mallinckrodt Chemical Works, was used without further purification. The checkers used Baker and Adamson anhydrous ether purchased from the Industrial Chemicals Division of Allied Chemical Company.
7. The checkers found that this preparation was equally successful when a solution of 0.50 mole of diethyl isopropylidenemalonate in 100 ml. of ether was added over 25 minutes to an ethereal solution of 0.55 mole of lithium dimethylcuprate. A solution of this reagent was prepared by adding 1.10 moles of methyllithium in ether solution (purchased from Foote Mineral Co., Exton, Pennsylvania) to a cold (−10°) suspension of 0.55 mole of copper(I) iodide in 200 ml. of anhydrous ether. The reaction mixture containing a suspension of yellow methylcopper was stirred at −5° for 5 minutes, then quenched with an aqueous mixture (pH 9) of ammonia and ammonium chloride. The product was isolated and distilled in the usual way, yielding 100 g. (93%) of the diethyl *tert*-butylmalonate, b.p. 57–61° (0.5–0.7 mm.), $n_D^{26.9}$ 1.4224.
8. The hydroiodic acid liberated during the hydrolysis step is frequently oxidized to iodine, which contaminates the final product. Washing the organic phase with aqueous sodium thiosulfate ensures the absence of this impurity in the final product.
9. The product has IR absorption (CCl_4) at 1750 cm.$^{-1}$ (ester C=O) with ^1H NMR peaks (CCl_4) at 1.08 (s, 9H), 1.22 (t, J = 7 Hz., 6H), 3.03 (s, 1H), and 4.05 (q, J = 7 Hz., 4H).

3. Discussion

Although diethyl *tert*-butylmalonate may be prepared in low yield by the alkylation of diethyl sodiomalonate with *tert*-butyl bromide[6] or *tert*-butyl chloride,[7] the alkylation of active methylene compounds such as malonic esters with *tert*-alkyl halides is normally a poor preparative procedure because of competing dehydrohalogenation of the alkyl halide.[8] A more satisfactory synthetic route to *tert*-alkyl derivatives of malonic esters and related compounds consists of the conjugate addition of alkyl- or arylmagnesium halides to alkylidenemalonates or alkylidenecyanoacetates.[8,9] Thus, diethyl *tert*-butylmalonate has been prepared in yields of 37–64% by the conjugate addition of methylmagnesium iodide to isopropylidenemalonate.[10,11]

The addition of copper salts was found to favor the conjugate addition of Grignard reagents to alkylidenemalonic esters,[12] and Munch-Peterson subsequently found that the addition of 1 mole % of copper(I) chloride was generally useful for promoting the addition of Grignard reagents to α,β-unsaturated esters.[13] The preformed copper(I) reagents such as the ether-soluble lithium dialkyl- or diarylcuprates are even more effective reactants in conjugate additions to α,β-unsaturated carbonyl compounds.[14] The present preparation illustrates the use of copper(I) chloride to catalyze the addition of methylmagnesium iodide to an alkylidenemalonic ester. In this case high yields of the conjugate addition product are obtained either by this procedure or by the use of lithium dimethylcuprate (Note 7). In a related preparation[15] successive addition of three moles of methylmagnesium iodide in the presence of copper(I) bromide to $(CH_3S)_2C{=}C(CO_2C_2H_5)_2$ proceeds with elimination of thiomethylmagnesium halide in the first two stages.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 762
- Org. Syn. Coll. Vol. 7, 346

References and Notes

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

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

tert-Butyl bromide (507-19-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

acetone (67-64-1)

copper(I) bromide (7787-70-4)

zinc chloride (7646-85-7)

tert-Butyl chloride (507-20-0)

hydroiodic acid (10034-85-2)

copper(I) chloride (7758-89-6)

Methyl iodide (74-88-4)

methylmagnesium iodide (917-64-6)

diethyl malonate (105-53-3)

diethyl sodiomalonate

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

Methyllithium (917-54-4)

copper(I)

lithium dimethylcuprate

Propanedioic acid, (1,1-dimethylethyl)-, diethyl ester,
Diethyl tert-butylmalonate (759-24-0)

Diethyl isopropylidenemalonate (6802-75-1)

methylcopper