A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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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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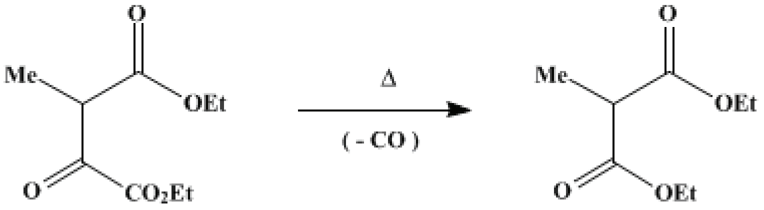
ETHYL METHYLMALONATE

[Malonic acid, methyl-, diethyl ester]

[(*A*) (*From Ethoxalylpropionic Ester*)]

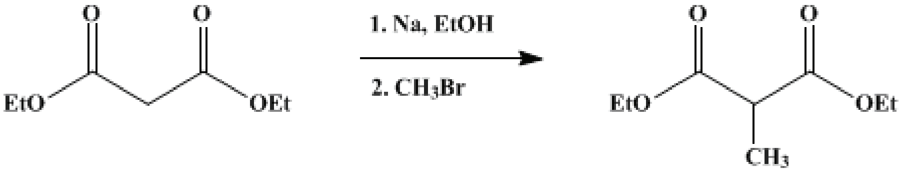


Submitted by Richard F. B. Cox and S. M. McElvain.
Checked by Reynold C. Fuson and William E. Ross.

1. Procedure

Three hundred forty-five grams (1.7 moles) of ethyl ethoxalylpropionate, b.p. 114–116°/10 mm. (p. 272), is placed in a round-bottomed flask of suitable size carrying a reflux condenser, and a thermometer is suspended from the top of the condenser into the liquid. The ethyl ethoxalylpropionate is then heated until a vigorous evolution of carbon monoxide begins (130–150°). The temperature of the liquid is gradually raised as the gas evolution diminishes, and finally the liquid is refluxed until no more gas comes off. The ethyl methylmalonate is then distilled. It boils at 194–196°/745 mm., and the yield is 288 g. (97 per cent of the theoretical amount).

[(*B*) (*From Malonic Ester*)]



Submitted by Nathan Weiner
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

Forty-six grams (2 gram atoms) of sodium, cut into small pieces, is added to 1 l. of absolute ethyl alcohol (Note 1) in a 2-l. three-necked flask equipped with a mechanical stirrer and a reflux condenser with a calcium chloride tube. When all the sodium is in solution, 320 g. (2 moles) of ethyl malonate (Note 2) is added. Then 200 g. (2.1 moles) of methyl bromide (Note 3) is bubbled into the stirred solution through a tube (at least 4 mm. in diameter) in the third neck of the flask which dips to the bottom of the solution.

The addition of the methyl bromide consumes about four hours. The reaction proceeds smoothly and with evolution of heat, occasionally reaching the boiling point of the mixture. During the course of the reaction sodium bromide separates. When the addition of methyl bromide is complete, the solution is pale orange and faintly alkaline. It is boiled for an additional half-hour then neutralized with glacial acetic acid and cooled. The sodium bromide is filtered with suction and washed on the funnel with a little cold alcohol. The major part of the alcohol is then removed by distillation at atmospheric pressure (Note 4). The sodium bromide is dissolved in 600–700 cc. of water containing 10 cc. of concentrated hydrochloric acid. The resulting solution (Note 5) is added to the residue from the distillation and the mixture shaken well. The aqueous lower layer is separated from the ester and extracted twice with ether. The ester and ether extracts are combined and dried by shaking quickly with calcium chloride and filtering immediately. The ether is removed, and the ester is shaken for exactly one minute with a cold solution of 10 g. of sodium hydroxide in 30 cc. of water (Note 6). The alkali is drawn off; the ester is washed with dilute acid and dried as before with calcium chloride. It is then distilled *in vacuo*, and the fraction boiling at 96°/16 mm. is taken. There is almost no fore-run or residue. The yield is 275–290 g. (79–83 per cent of the theoretical amount).

2. Notes

1. The quality of the alcohol is very important, traces of water depressing the yield considerably. Absolute alcohol, as ordinarily supplied, is best dried by distillation from a 2–3 per cent solution of sodium, a fore-run and the last 25 per cent being rejected.

2. Even the better grades of malonic ester have been found to contain sufficient impurities to decrease the yield. However, one distillation, at reduced pressure, of even the technical grade of malonic ester makes it sufficiently pure for this synthesis.

3. Vials of methyl bromide may be conveniently used by cooling in an ice bath, breaking the seal, and attaching to the delivery tube by means of ordinary rubber tubing. The vial is then allowed to come to room temperature, and the evaporation of the liquid keeps it sufficiently cool so that it enters the solution at the desired rate. It is best to dry the gas by passage through a tower of potassium hydroxide pellets.

If methyl bromide is not available, it may be generated as follows: 500 g. of 95 per cent sulfuric acid is added slowly, with shaking, to 400 g. of ordinary methyl alcohol, cooled by an ice bath. Six hundred grams of sodium bromide is suspended in one half of this mixture in a 1-l. round-bottomed flask, fitted with a two-holed stopper holding a dropping funnel and a delivery tube. The evolution of methyl bromide is started by heating the flask with a water bath at 50°, and the remainder of the methyl alcohol-acid mixture is added slowly from the funnel as the volume of the mixture in the flask decreases. As the rate of evolution of the gas falls off the temperature is slowly raised until no more methyl bromide is generated and the contents of the flask have become completely solid. The flask is shaken from time to time during the generation to mix the components more thoroughly. The evolved gas is dried by passage through a tower of potassium hydroxide pellets.

4. The removal of the alcohol at atmospheric pressure is best carried out by returning the filtrate to the original reaction flask, in which the mechanical stirrer is retained but the reflux condenser is replaced by a goose-neck and a condenser for downward distillation. The solution is stirred as the alcohol is distilled, thus eliminating the violent bumping that would otherwise occur at the separation of sodium bromide from the concentrated solution.

5. The use of the sodium bromide in this way serves the multiple purpose of releasing any ester that may be adsorbed on it, of depressing the solubility of the ester in the water, and of making the water layer sufficiently dense for the ester to float on it.

6. The ester is treated in this manner to remove any unchanged ethyl malonate. Michael[1] has shown that this treatment will completely remove unchanged ethyl malonate while hardly attacking ethyl methylmalonate. No ethyl dimethylmalonate is formed when methyl bromide is used as the methylating agent.

3. Discussion

The most widely used method of preparing ethyl methylmalonate is by the alkylation of ethyl malonate with methyl iodide,[2], [1] methyl bromide,[3] or methyl sulfate.[4] A separation of the desired product from traces of unchanged starting material and from ethyl dimethylmalonate cannot be accomplished by distillation as the boiling points of the three esters lie within three and one-half degrees of one another. Michael[1] found that unchanged malonic ester can be removed completely by taking advantage of the greater ease with which it is hydrolyzed by alkali, while Gane and Ingold[5] obtained a pure product by hydrolysis, crystallization of the methylmalonic acid, and re-esterification. It can be inferred from the results of Salkowski, Jr.,[6] with acetoacetic ester that no disubstitution occurs when methyl bromide is employed as the alkylating agent. Procedure *B* above, which is based on the work of Michael,[1] has been published.[7]

Pure ethyl methylmalonate can also be prepared by the reduction of methylidenemalonic ester with Raney nickel;[8] from ethyl α-bromopropionate through the nitrile,[9] an expensive process because of the cost of the materials and the poor yields; and by the pyrolysis of ethyl ethoxalylpropionate. This last method, which forms the basis for Procedure *A* above, was first described by Wislicenus.[10]

References and Notes

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

acetoacetic ester

ETHYL ETHOXALYLPROPIONATE

Ethoxalylpropionic Ester

Malonic Ester

methylidenemalonic ester

ethyl alcohol,
alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

sodium bromide (7647-15-6)

Raney nickel (7440-02-0)

sodium (13966-32-0)

methyl bromide (74-83-9)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

ethyl malonate (1071-46-1)

Ethyl methylmalonate

Malonic acid, methyl-, diethyl ester (609-08-5)

ethyl dimethylmalonate

methylmalonic acid (516-05-2)

ethyl α-bromopropionate (535-11-5)