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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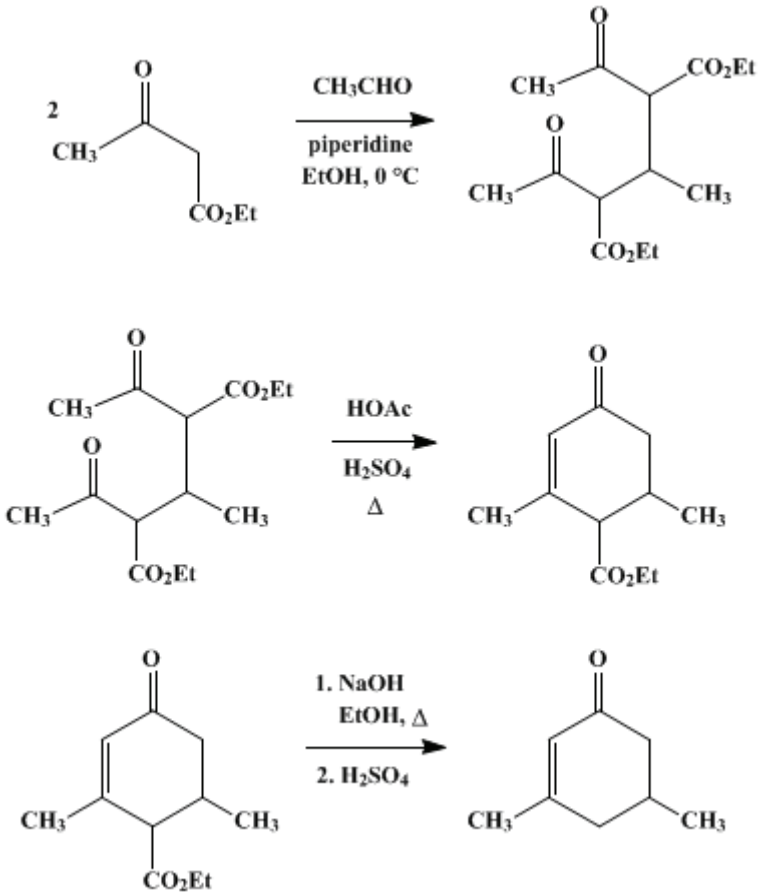
3,5-DIMETHYL-4-CARBETHOXY-2-CYCLOHEXEN-1-ONE and 3,5-DIMETHYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 4-carbethoxy-3,5-dimethyl-, and 2-cyclohexen-1-one, 3,5-dimethyl-]



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1. Procedure

A. 3,5-*Dimethyl*-4-*carbethoxy*-2-*cyclohexen*-1-*one*. In each of three 500-ml. Erlenmeyer flasks (Note 1) is placed 210 ml. (210 g., 1.61 mole) of ethyl acetoacetate (Note 2). The flasks are placed in an ice-salt bath and chilled to 0°; to each flask there is then added 45 ml. (35.2 g., 0.78 mole) of acetaldehyde. When the contents of the flasks have cooled to −5° to 0° there is added to each flask, with shaking, a solution of 2 ml. of piperidine in 5 ml. of absolute ethanol. The flasks, the contents of which become cloudy in a short time because of the separation of water, are kept in the ice-salt bath for 6 hours. The reaction mixtures are then combined in a 1-l. flask and placed in an icebox. About 24 hours later, 3 ml. of piperidine in 5 ml. of absolute ethanol is added with shaking, and the flask is replaced in an icebox until the next day. The addition of 3 ml. of piperidine in 5 ml. of absolute ethanol is repeated once more, and the mixture is again returned to the icebox for 24 hours. The mixture is then allowed to stand for at least 1 day at room temperature. At some point during this reaction period the mixture should crystallize as a mass of yellow-white needles (Note 3). This product is crude ethyl ethylidenebisacetoacetate.

The crude bis ester is melted on a steam cone and poured into a 3-l. round-bottomed flask containing 600 ml. of glacial acetic acid, 40 ml. of concentrated sulfuric acid, and approximately 10 g. of small chips of porous plate (Note 4). The mixture is heated under reflux for 1 hour. There is a copious evolution of carbon dioxide which should be directed to a gas-absorption trap since it is accompanied by acetic acid vapors. The mixture is poured, with mechanical stirring, into 2 l. of ice water in a 4-l. beaker. Enough ether is added to allow separation of the layers (Note 5), and the organic layer is returned to the beaker with 1.2–1.3 l. of water. With the aid of good stirring the mixture is neutralized by slow addition of solid sodium carbonate until the effervescence ceases. The layers are separated, and the material so obtained may be used immediately for the preparation of 3,5-dimethyl-2-cyclohexen-1-one. To obtain 3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one, the ether solution is washed with 100 ml. of 5% sodium hydroxide solution and then with 100 ml. of water containing 2 ml. of acetic acid, is dried over anhydrous magnesium sulfate, and distilled through a short column under reduced pressure. After a very slight fore-run the main fraction is collected at 135–155°/10 mm. This is redistilled through a moderately good column, preferably of the Widmer or Vigreux type. The product is 3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one, b.p. 136–138°/9 mm. The yield is 220–234 g. (47–50%).

B. 3,5-*Dimethyl*-2-*cyclohexen*-1-*one*. The ether solution of crude 3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one obtained as described above is transferred to a 3-l. round-bottomed flask. The ether is removed on a steam cone, perferably with the aid of an aspirator, and there are added 1140 ml. of water, 60 ml. of ethanol (95%), and 130 g. of sodium hydroxide. The mixture is shaken continuously and heated on a steam cone until the alkali dissolves, and heating is continued on a steam cone with frequent shaking until the ester dissolves (Note 6). The solution is then refluxed for 15 minutes.

The flask is cooled with a stream of water while a solution of 100 ml. of concentrated sulfuric acid in 200 ml. of water is added slowly and cautiously (Note 7). The acidified mixture is heated under reflux for 15 minutes, allowed to cool, and the layers are separated. The crude product is diluted with 100 ml. of ether and washed successively with two 100-ml. portions of 5% sodium hydroxide solution and with 100 ml. of water containing 5 ml. of acetic acid. The ethereal solution, after drying over anhydrous magnesium sulfate, is distilled through a short column under reduced pressure. The product boiling at 84–86°/9 mm. is 3,5-dimethyl-2-cyclohexen-1-one; the yield is 155–165 g. (52–55%) (Note 8).

2. Notes

1. The checkers found it more convenient to use a 1-l. Erlenmeyer flask instead of three 500-ml. flasks.
2. The ethyl acetoacetate was obtained from the Carbide and Carbon Chemicals Company. The acetaldehyde was obtained from the Niacet Chemicals Corporation. The piperidine was the Practical grade of the Eastman Kodak Company.
3. Crystals may appear before the addition of all the piperidine has been completed. In this even the time of standing as described is followed, but no more catalyst need be added.
4. Ordinary boiling chips are convenient.
5. Usually 150–200 ml. of ether is ample. The layers may be separated in a separatory funnel, or the lower aqueous layer may be removed with a siphon.
6. The solution of the ester is an exothermic process. No attempt should be made to heat the mixture to reflux temperature until the ester has been dissolved.
7. It is important that this step be carried out slowly and with a hot solution. A satisfactory method is to place the flask in a sink while the contents are still hot and to cool with a stream of water directed over the entire flask. The sulfuric acid solution should be poured slowly down the wall of the flask, the rate of addition being regulated by the vigor of the decarboxylation. It is possible to carry out part of the decarboxylation in the alkaline solution by prolonging the reflux period, but this procedure offers no advantage over that described.
8. This general procedure can also be applied to compounds derived from other aliphatic aldehydes.[1]

3. Discussion

3,5-Dimethyl-4-carbethoxy-2-cyclohexen-1-one and 3,5-dimethyl-2-cyclohexen-1-one are usually

prepared from acetaldehyde and acetoacetic ester through the Knoevenagel condensation.[2] The keto ester has been obtained previously by selective saponification and decarboxylation methods which have involved heating the crude condensation product with water at 140°[2,3] or with sodium ethoxide in ethanol.[3] The ketone has also been obtained from the same condensation product by prolonged refluxing in 20% sulfuric acid.[2,4,5] 3,5-Dimethyl-2-cyclohexen-1-one has also been obtained by the reduction of 2,4,6-trimethylpyridine with sodium and ethanol in liquid amomnia, followed by hydrolysis and cyclization.[6]

References and Notes

1. Horning, Denekas, and Field, *J. Org. Chem.*, **9**, 548 (1944).
2. Knoevenagel, *Ann.*, **281**, 104 (1894).
3. Rabe, *Ann.*, **342**, 344 (1905).
4. Gatterman, *Practical Methods of Organic Chemistry*, trans. by Schober and Babasinian, p. 202, The Macmillan Company, New York, 1921.
5. Smith and Roualt, *J. Am. Chem. Soc.*, **65**, 634 (1943).
6. Birch, *J. Chem. Soc.*, **1947**, 1270.

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

ethanol (64-17-5)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

sodium (13966-32-0)

piperidine (110-89-4)

sodium ethoxide (141-52-6)

Ethyl acetoacetate (141-97-9)

magnesium sulfate (7487-88-9)

3,5-Dimethyl-4-carbethoxy-2-cyclohexen-1-one,

2-Cyclohexen-1-one, 4-carbethoxy-3,5-dimethyl- (6102-15-4)

3,5-Dimethyl-2-cyclohexen-1-one,
2-cyclohexen-1-one, 3,5-dimethyl- (1123-09-7)

ethyl ethylidenebisacetoacetate

2,4,6-trimethylpyridine (108-75-8)