



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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

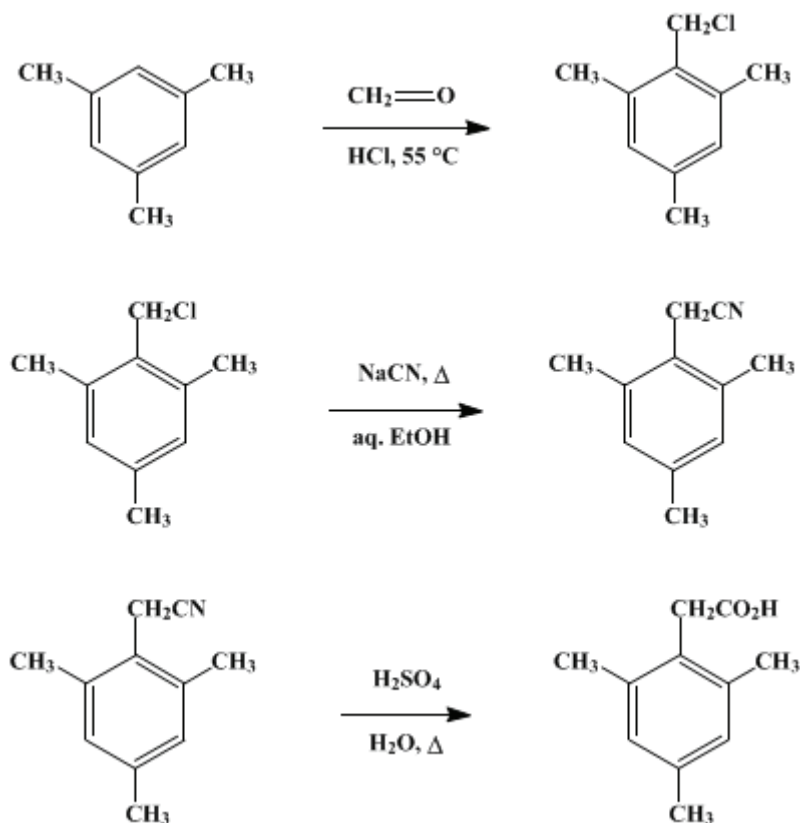
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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.557 (1955); Vol. 25, p.65 (1945).

MESITYLACETIC ACID

[Acetic acid, mesityl-]



Submitted by Reynold C. Fuson and Norman Rabjohn.

Checked by W. E. Bachmann, E. L. Jenner, and G. Dana Johnson.

1. Procedure

A. *α^1 -Chloroisodurene*. In a 2-l. round-bottomed flask, equipped with a sealed mechanical stirrer (Note 1), a gas inlet tube, and a reflux condenser, are placed 200 g. (1.66 moles) of mesitylene, 1 l. of concentrated hydrochloric acid, and 63 ml. (0.84 mole) of formaldehyde solution (concentration, 37%) (Note 2). Hydrogen chloride is introduced below the surface of the mixture (Note 3), which is stirred vigorously and heated in a water bath kept at 55°. These conditions are maintained throughout the reaction, which requires a total of 5.5 hours. At the halfway point, an additional 63 ml. (0.84 mole) of formaldehyde solution is added (Note 4).

After the mixture has been cooled to room temperature (Note 5), it is extracted with three 300-ml. portions of benzene. The combined benzene extracts are washed successively with water, dilute sodium hydroxide, and water, dried over calcium chloride, and filtered. The mixture is distilled through a still head under reduced pressure; the pressure is reduced only slightly while the benzene is distilling. The yield of α^1 -chloroisodurene boiling at 130–131°/22 mm. is 155–170 g. (55–61%) (Note 6); the distillate solidifies to a crystalline mass which melts at 37°.

B. *Mesitylacetonitrile*. In a 1-l. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel, are placed 77 g. (1.57 moles) of sodium cyanide, 110 ml. of water, and 160 ml. of ethanol. The flask is heated in a boiling water bath, and the contents are stirred until all the sodium cyanide is dissolved. Then 152 g. (0.90 mole) of α^1 -chloroisodurene is added slowly, and

stirring and heating are continued for 3 hours.

The reaction mixture is allowed to cool to about 40° (Note 7) and extracted with three 300-ml. portions of benzene. The benzene solution is washed well with water, dried over calcium chloride, filtered, and distilled under slightly reduced pressure to remove all the benzene. The residue is then distilled under reduced pressure from a Claisen flask with a wide-bore side arm. The yield of mesitylacetonitrile boiling at 160–165°/22 mm. is 128–133 g. (89–93%) (Note 8). This product is sufficiently pure for the next step. When recrystallized from petroleum ether, it melts at 79–80°.

C. *Mesitylacetic acid*. To 900 ml. of water in a 3-l. three-necked flask is added 750 ml. of concentrated sulfuric acid. When the mixture has cooled to about 50°, 127 g. (0.80 mole) of mesitylacetonitrile is added (Note 9), and the mixture is refluxed and stirred mechanically for 6 hours. At the end of this period, a large amount of mesitylacetic acid has precipitated from the solution. The contents of the flask are cooled and poured into 3 l. of ice water. The acid is collected on a Büchner funnel and washed well with water. A solution of the acid in dilute alkali is boiled with Norit, and the acid is precipitated from the filtered solution by acidifying with dilute hydrochloric acid. The mesitylacetic acid is collected on a filter, washed well with water, and dried in an oven at about 80°. The yield of mesitylacetic acid melting at 163–166° is 123 g. (87%). After recrystallization from dilute alcohol or ligroin, the acid melts at 167–168°.

2. Notes

1. The checkers used an Ace Tru-bore stirrer. This convenient sealed stirrer, which owes its seal to the snug fit between a ground-glass section of the stirrer shaft and a ground-glass bearing, can be obtained from the Ace Glass Company, Vineland, New Jersey.
2. Commercial formalin was used. This aqueous-methanolic solution contains 37% formaldehyde by weight. It is sometimes called "40% formalin" because 100 ml. of the solution contains 40 g. of formaldehyde.
3. The hydrogen chloride is introduced at such a rate that the bubbles form a little faster than they can be counted.
4. The yield of monochloromethyl compound seems to be improved slightly by adding the formalin in two portions instead of introducing the entire amount at the beginning of the reaction.
5. If the reaction mixture is cooled to too low a temperature, the chloromethyl derivatives will solidify. It is much easier to carry out the extractions while the mixture is still liquid.
6. The residue consists chiefly of α^1, α^2 -dichloropentamethylbenzene. The fraction boiling at 131–200°/22 mm. is collected and recrystallized from petroleum ether; m.p. 105°.
7. If the reaction mixture is allowed to cool much below this temperature, it will solidify in the flask.
8. This method has been applied successfully to the preparation of 2,4,6-triethylphenylacetone nitrile (b.p. 127°/3–4 mm.; yield, 72%); durylacetonitrile (m.p. 80–81°; yield, 75%); and isodurylacetonitrile (m.p. 74–75°; yield, 74%).
9. If the mesitylacetonitrile has not been purified by distillation, or if it is added to a boiling solution of sulfuric acid, the reaction mixture has a tendency to become very dark.

3. Discussion

α^1 -Chloroisodurene can be prepared by the action of chloromethyl ether on mesitylene in the presence of stannic chloride³ or acetic acid.¹ The procedure described is based on that of Nauta and Dienske.⁴

Mesitylacetonitrile can be prepared by the action of potassium cyanide on α^1 -chloroisodurene² or by treating α^1 -chloroisodurene with cuprous cyanide in the presence of pyridine.⁵ The procedure described is based upon the method for the preparation of benzyl cyanide from benzyl chloride.

Mesitylacetic acid has been prepared from 2,4,6-trimethylacetophenone by treatment with yellow ammonium sulfide and hydrolyzing the resulting amide with alkali,⁶ by the dry distillation of 2,4,6-trimethylmandelic acid,⁷ by heating 2,4,6-trimethylphenylglyoxylic acid with hydriodic acid and red phosphorus⁸ or with hydrazine hydrate,⁹ by the action of boiling water on mesityldiazomethane¹⁰ (prepared in turn from mesitylglyoxal monohydrazone), and by treating mesitylacetonitrile with

References and Notes

1. Vavon and Bolle, *Compt. rend.*, **204**, 1826 (1937).
 2. Hoch, *Compt. rend.*, **192**, 1464 (1931).
 3. Sommelet, *Compt. rend.*, **157**, 1443 (1913).
 4. Nauta and Dienske, *Rec. trav. chim.*, **55**, 1000 (1936).
 5. Newman, *J. Am. Chem. Soc.*, **59**, 2472 (1937).
 6. Claus, *J. prakt. Chem.*, (2) **41**, 508 (1890); Willgerodt, *J. prakt. Chem.*, (2) **80**, 185 (1909); Willgerodt and Merk, *J. prakt. Chem.*, (2) **80**, 193 (1909).
 7. Meyer and Molz, *Ber.*, **30**, 1274 (1897).
 8. Dittrich and Meyer, *Ann.*, **264**, 140 (1891).
 9. Lock, *Oesterr. Chem. Ztg.*, **51**, 77 (1950) [*C. A.*, **44**, 8338 (1950)].
 10. Fuson, Armstrong, and Shenk, *J. Am. Chem. Soc.*, **66**, 964 (1944).
-

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

red phosphorus

ligroin

petroleum ether

durylacetonitrile

isodurylacetonitrile

2,4,6-trimethylacetophenone

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

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

acetic acid (64-19-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

formaldehyde,
formalin (630-08-0)

sodium cyanide (143-33-9)
Cuprous Cyanide (544-92-3)
potassium cyanide (151-50-8)
Norit (7782-42-5)
pyridine (110-86-1)
potassium hydroxide (1310-58-3)
benzyl chloride (100-44-7)
Benzyl cyanide (140-29-4)
hydriodic acid (10034-85-2)
Mesitylene (108-67-8)
hydrazine hydrate (7803-57-8)
ammonium sulfide
chloromethyl ether (542-88-1)
stannic chloride (7646-78-8)
2,4,6-trimethylphenylglyoxylic acid (3112-46-7)
2,4,6-trimethylmandelic acid
Mesitylacetic acid,
Acetic acid, mesityl- (4408-60-0)
mesitylacetonitrile (34688-71-6)
2,4,6-triethylphenylacetonitrile
mesityldiazomethane
mesitylglyoxal monohydrazone