Organic Syntheses

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.

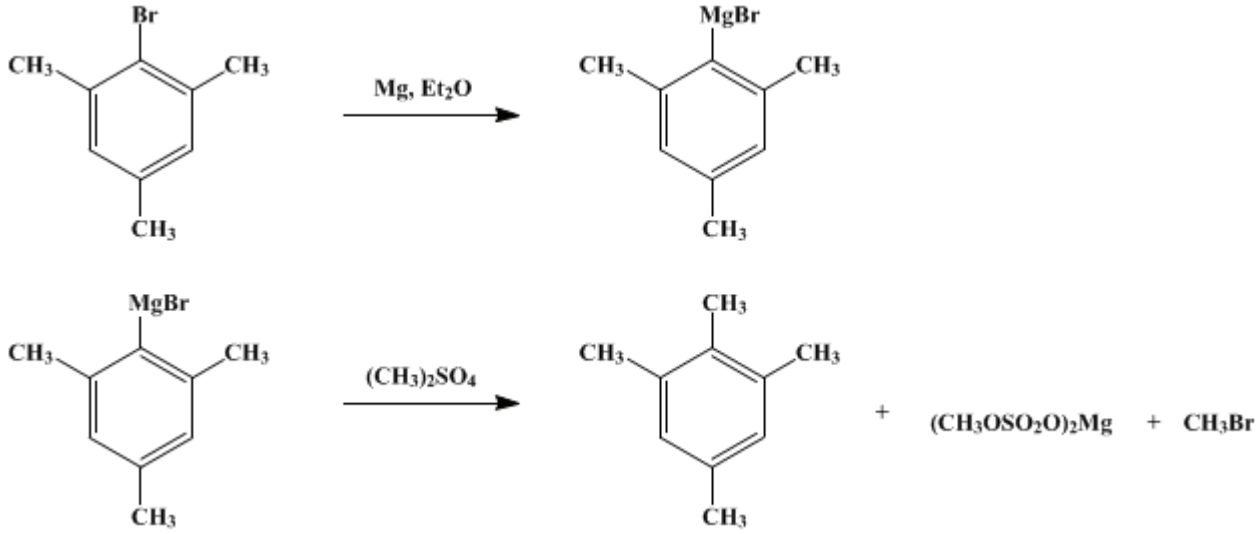
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries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

DOI:10.15227/orgsyn.011.0066

Organic Syntheses, Coll. Vol. 2, p.360 (1943); Vol. 11, p.66 (1931).

ISODURENE



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1. Procedure

A 3-l. three-necked flask fitted with a reflux condenser protected from the air by a calcium chloride tube, a separatory funnel, and a mechanical stirrer is mounted on a steam bath. In the flask are placed 48 g. (2 moles) of magnesium turnings, 150 cc. of anhydrous ether and 100 g. of bromomesitylene (p. 95). The reaction starts slowly, and sometimes it is necessary to add some iodine or use Gilman's catalyst (Note 1). After the reaction starts, it proceeds smoothly and the remaining 298 g. of bromomesitylene (a total of 2 moles) in about 700 cc. of dry ether is added at such a rate that the ether boils briskly. After the last of this ether solution has been added, the mixture is heated on the steam cone until practically all the magnesium has dissolved (Note 2).

The solution of the Grignard reagent is cooled to about 10°, and to it, while stirring vigorously, is added a solution of 600 g. (4.8 moles) of methyl sulfate (Note 3) in about 500 cc. of dry ether. The reaction is very vigorous, and bumping may occur as the result of the separation of insoluble magnesium compounds. The addition of the methyl sulfate requires two to three hours. The reaction mixture is allowed to stand (Note 4) for about twenty-four hours and is then decomposed by adding dilute hydrochloric acid through the separatory funnel. Stirring is started as soon as the mass is fluid enough. When the mixture is decomposed completely, the ether layer is separated and washed three times with water. After the magnesium salts have been removed, the ether layer is evaporated and the residue is added slowly to a solution of 30 g. of sodium in 500 cc. of absolute alcoholx (Note 5). The mixture is boiled for about one-half hour. Then the solution is cooled, 150–200 cc. of ether is added, and the alkali and alcohol are removed by washing thoroughly with water (Note 6). Finally the ether solution is dried over calcium chloride, the ether is distilled, and the residue is warmed on a water bath for three to four hours with 25–30 g. of metallic sodium (Note 7). The mixture is filtered, and the filtrate is fractionated carefully under reduced pressure in a modified Claisen flask. The fractions collected are: up to 85°/18 mm.; 85–87°/18 mm.; and residue. The low-boiling fraction weighs about 50 g. and is mainly mesitylene. The second fraction is isodurene and has a melting point of −24.2°. The yield is 140–160 g. (52–60 per cent of the theoretical amount).

2. Notes

1. Gilman's catalyst[1] is prepared readily by heating an alloy of magnesium containing 12.75 per cent of

copper with about 20 per cent by weight of iodine in an evacuated flask. Only about 0.25 g. of this catalyst is required to bring about a reaction with a halogen compound. When this catalyst is used, the ordinary magnesium turnings are added as soon as the reaction has started. The reaction can also be started by adding a small amount of an ether solution of any Grignard reagent, such as ethylmagnesium bromide.
2. If Gilman's catalyst is used to start the reaction there will always be an excess of magnesium at the end of the reaction.
3. The methyl sulfate was distilled carefully under reduced pressure, and a fraction boiling within 1° was used.
Methyl sulfate is extremely toxic, and great care must be taken to avoid breathing the vapors and spilling the liquid on the hands or clothes. Ammonia is a specific antidote for methyl sulfate.
4. The reaction mixture sometimes becomes almost solid; stirring is then useless.
5. Aqueous alkali is not sufficient to remove the excess methyl sulfate. Sometimes the reaction between the excess methyl sulfate and the sodium ethoxide solution is vigorous; therefore the two solutions should be mixed carefully. If a large excess of methyl sulfate is present, more sodium ethoxide may be needed in order to keep the solution alkaline.
6. Emulsions can be broken by acidifying.
7. The treatment with sodium ensures a halogen-free product.

3. Discussion

Isodurene has been prepared from bromomesitylene, methyl iodide, and sodium;[2] from mesitylene, methyl chloride, and aluminum chloride;[3] from mesitylene, methyl iodide, aluminum chloride, and carbon disulfide;[4] from 1,3,4,5-tetramethylbenzonitrile with hydrogen chloride at 250°;[5] by the action of zinc chloride or iodine on camphor;[6] and in small amounts by the action of concentrated sulfuric acid on acetone.[7] The method of preparation described above has been published.[8]

Methods of preparation in which aluminum chloride is used do not give a pure product; aluminum chloride shifts the methyl groups to give mixtures of the three tetramethylbenzenes from which isodurene cannot be separated efficiently. Compare Note 7, p. 252.

References and Notes

1. Gilman, Peterson, and Schulze, Rec. trav. chim. **47**, 19 (1928)
2. Jannasch, Ber. **8**, 356 (1875); Bielefeldt, Ann. **198**, 380 (1879); Jannasch and Weiler, Ber. **27**, 3442 (1894).
3. Jacobsen, ibid. **14**, 2629 (1881).
4. Claus and Foecking, ibid. **20**, 3097 (1887).
5. Hofmann, ibid. **17**, 1915 (1884).
6. Armstrong and Miller, ibid. **16**, 2259 (1883).
7. Orndorff and Young, Am. Chem. J. **15**, 267 (1893).
8. Smith and MacDougall, J. Am. Chem. Soc. **51**, 3003 (1929).

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

Gilman's catalyst

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

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

ammonia (7664-41-7)

ether (60-29-7)

magnesium,
magnesium turnings (7439-95-4)

methyl chloride (74-87-3)

copper (7440-50-8)

iodine (7553-56-2)

acetone (67-64-1)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

carbon disulfide (75-15-0)

zinc chloride (7646-85-7)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

Mesitylene (108-67-8)

ethylmagnesium bromide (925-90-6)

Bromomesitylene (27129-86-8)

Isodurene (527-53-7)

1,3,4,5-tetramethylbenzonitrile

camphor (21368-68-3)