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.

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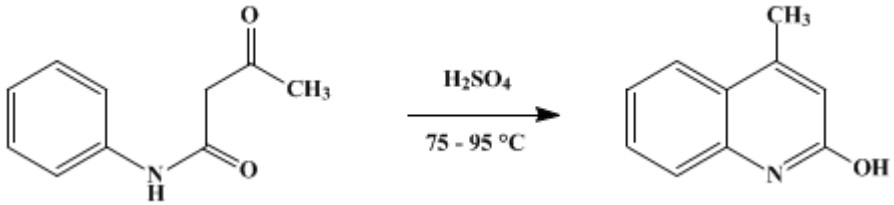
4-METHYLCARBOSTYRIL

[Carbostyril, 4-methyl-]



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1. Procedure

One hundred seventy-seven grams (1 mole) of acetoacetanilide is added in small portions by means of a spatula to 185 ml. of concentrated sulfuric acid which has been heated previously to 75° (Note 1) in a 1-l. three-necked flask provided with a mechanical stirrer and a thermometer which extends into the liquid. The temperature of the mixture is maintained at 70–75° by intermittent cooling until nearly all the acetoacetanilide has been added. The last 10–15 g. is added without cooling, and the temperature rises to 95°; the addition requires 20–30 minutes. The heat of reaction maintains the temperature at 95° for about 15 minutes; the reaction mixture is then kept an additional 15 minutes at 95° by external heating. After the solution has cooled to 65°, it is poured into 5 l. of water with vigorous stirring.

After cooling, the product is filtered by suction, washed with four 500-ml. portions of water and two 250-ml. portions of methanol, and air-dried. The yield of 4-methylcarbostyril is 138–144 g. (86–91%). This material, which melts at 219–221°, is suitable for preparing 2-chlorolepidine (p. 194). It may be purified further by recrystallization from 95% ethanol. For recrystallization 39 g. is dissolved in 650 ml. of solvent; the recovery is 33–33.5 g., and the melting point of the product is 222–224°.

2. Notes

1. The reaction flask must be so situated that it can be cooled rapidly. The submitter reports that the yield was reduced to 72% in one run in which the temperature reached 120°.

3. Discussion

The only useful method for preparing 4-methylcarbostyril is that of Knorr,[1] described by Mikhailov.[2] Two modifications include the use of aniline and ethyl acetoacetate, without isolation of acetoacetanilide,[3] and the use of boron trifluoride as a cyclization agent.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 194

References and Notes

1. Knorr, *Ann.*, **236**, 83 (1886).
2. Mikhailov, *J. Gen. Chem. U.S.S.R.*, **6**, 511 (1936) [*C. A.*, **30**, 6372 (1936)].
3. Hauser and Reynolds, *J. Am. Chem. Soc.*, **70**, 2402 (1948).
4. Killelea, *J. Am. Chem. Soc.*, **70**, 1971 (1948).

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

ethanol (64-17-5)

sulfuric acid (7664-93-9)

methanol (67-56-1)

aniline (62-53-3)

Ethyl acetoacetate (141-97-9)

boron trifluoride (7637-07-2)

Acetoacetanilide (102-01-2)

2-Chlorolepidine (634-47-9)

4-Methylcarbostyril,
Carbostyril, 4-methyl- (607-66-9)