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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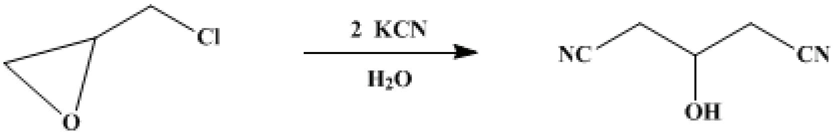
3-HYDROXYGLUTARONITRILE

[Glutaronitrile, 3-hydroxy-]



Submitted by F. Johnson and J. P. Panella[1].
Checked by A. G. Anastassiou and B. C. McKusick.

1. Procedure

A mixture of 493 g. (2.00 moles) of magnesium sulfate heptahydrate and 700 ml. of tap water is stirred for 5 minutes and filtered into a 2-l. three-necked flask equipped with a mechanical stirrer and an alcohol thermometer that dips into the solution. The flask is immersed in a cooling bath (Note 1), the stirrer is started, and the solution is cooled to 10°. To the solution is added, in one portion, 143 g. (2.20 moles) of potassium cyanide *(Caution! Toxic)*, and stirring is continued for 45 minutes at 8–12° (Note 2). The solution is maintained at this temperature while 102 g. (1.10 moles) of epichlorohydrin (Note 3) is added dropwise with stirring over a period of 1 hour (Note 4). The mixture is allowed to come to room temperature and is stirred for an additional 24 hours at this temperature.

The dark red-brown reaction mixture is stirred and extracted continuously with 1 l. of ethyl acetate for 48 hours (Note 5). The extract is dried over anhydrous magnesium sulfate for 18 hours (Note 6), filtered, and the filtrate is concentrated under reduced pressure on a steam bath. The residual dark-brown oil (about 90 g.) is distilled from a Claisen flask; the distillation must be rapid to minimize decomposition. About 20 g. of fore-run consisting of 4-chloro-3-hydroxybutyronitrile and 4-hydroxycrotononitrile is collected at 90–115° (0.4 mm.). 3-Hydroxyglutaronitrile is collected at 155–160° (0.4 mm.), yield 65–75 g. (54–62%), $n^{23}\mathrm{D}$ 1.4634. This pale yellow distillate is sufficiently pure for most purposes. Further purification can be effected with only 3–5% loss by distillation of the material through a 15-cm. Vigreux column and collection of the portion boiling at 154–156° (0.2 mm.), $n^{23}\mathrm{D}$ 1.4632 (Note 7).

2. Notes

1. The bath contained a mixture of trichloroethylene and solid carbon dioxide kept at −20°.
2. At this point the mixture has an opaque milky-white appearance caused by precipitation of a little magnesium hydroxide.
3. Epichlorohydrin (white label brand) supplied by Eastman Organic Chemicals was used without further purification.
4. The reaction is exothermic. If the temperature of the reaction mixture is allowed to rise above 30°, the reaction is likely to get out of control.
5. The checkers found that a stirred extractor[2] was much more efficient than an unstirred one for this operation.
6. This extensive drying period is necessary to allow precipitation of traces of basic salts that have been carried over during the extraction procedure. Failure to remove these salts results in extensive decomposition of the product during the distillation step.
7. The submitters have obtained the same yield working on 10 times this scale.

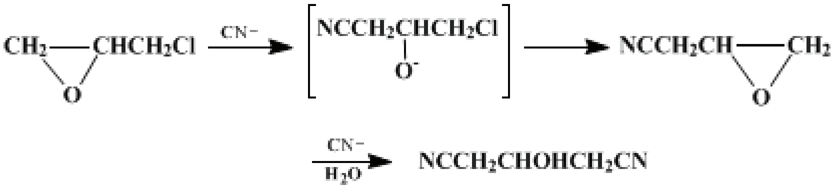
3. Discussion

3-Hydroxyglutaronitrile has been prepared by the action of potassium cyanide on 1,3-dichloro-2-propanol[3,4,5] or on 4-chloro-3-hydroxybutyronitrile.[6,7] More recently it has been prepared from epichlorohydrin using essentially the present method.[8]

4. Discussion

This is a much more convenient and satisfactory synthesis of 3-hydroxyglutaronitrile than earlier ones.[3,4,5,6,7] The method can be applied to other epichlorohydrins; 2-methylepichlorohydrin and 2-ethylepichlorohydrin have been converted to the corresponding hydroxydinitriles in 71% and 77% yields, respectively.[8] The hydroxydinitriles undergo cyclizations to heterocyclic compounds not easily prepared in other ways. Thus hydrogen bromide at 0° converts 3-hydroxyglutaronitrile to 2-amino-6-bromopyridine in 70% yield.[9]

The reaction probably proceeds as follows:[8]



References and Notes

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

2-methylepichlorohydrin

2-ethylepichlorohydrin

ethyl acetate (141-78-6)

Epichlorohydrin (106-89-8)

hydrogen bromide (10035-10-6)

potassium cyanide (151-50-8)

carbon dioxide (124-38-9)

magnesium hydroxide

1,3-dichloro-2-propanol (96-23-1)

magnesium sulfate (7487-88-9)

trichloroethylene (79-01-6)

3-Hydroxyglutaronitrile,
Glutaronitrile, 3-hydroxy- (13880-89-2)

magnesium sulfate heptahydrate (10034-99-8)

4-chloro-3-hydroxybutyronitrile

4-hydroxycrotononitrile

2-amino-6-bromopyridine