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.

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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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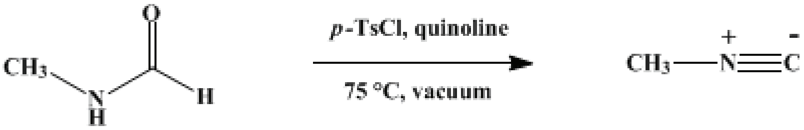
METHYL ISOCYANIDE



Submitted by R. E. Schuster, James E. Scott, and Joseph Casanova, Jr.[1].
Checked by John A. Dupont and William D. Emmons.

1. Procedure

Caution! Methyl isocyanide should be prepared in a good hood since it is toxic and has a very unpleasant odor. The reaction and subsequent distillation of the product should be conducted behind safety shields (Note 1).

In a 2-l. four-necked flask (Note 2) equipped with a 250-ml. pressure-equalizing dropping funnel, a sealed mechanical stirrer, a thermometer, and a receiver trap (Note 3) are placed 1034 g. (8.0 moles) of quinoline and 572 g. (3.0 moles) of *p*-toluenesulfonyl chloride (Note 4). The solution is heated to 75° by an oil bath and the system evacuated to a pressure of 15 mm. The receiver is cooled in a bath of liquid nitrogen (Note 5). While the solution is vigorously stirred and maintained at this temperature, 118 g. (2.0 moles) of N-methylformamide (Note 4) is added dropwise to maintain a smooth distillation rate. The addition is complete in 45–60 minutes.

The material which collects in the receiver is distilled through a 15-cm. Vigreux column at atmospheric pressure. Methyl isocyanide, a colorless, vile-smelling liquid, is collected at 59–60°; weight 57–61 g. (69–74%) (Note 6). Analysis by gas liquid chromatography indicates that the purity exceeds 99% (Note 7).

2. Notes

1. An explosion involving methyl isocyanide has been reported.[2] For this reason, prudence dictates the use of adequate shielding in all heating operations.
2. A three-necked flask may be used by employing a suitable adapter on one of the necks. The checkers used a standard wide-bore, 75-degree side-arm adapter fitted with a long-stemmed thermometer extending into the reaction solution. A Trubore® stirrer equipped with a semicircular Teflon® paddle was also used.
3. A vapor trap having a wide-bore inlet tube and the appropriate condensate capacity is used. The checkers used a 4.8 cm. × 30.0 cm. trap having a 2.0 cm. × 18.0 cm. inlet tube. Best results are obtained when the trap is connected directly to the flask or the adapter (see (Note 2)) by a wide-bore tube. Ground-glass joints should be used throughout the apparatus.
4. All materials were obtained from Eastman Kodak Company. Quinoline, practical grade, b.p. 72–74° (0.2 mm.), was freshly distilled from zinc dust. If undistilled quinoline is employed, a major contaminant, which appears to be methyl isocyanate, will be formed. "White label" *p*-toluenesulfonyl chloride and N-methylformamide were used without further purification.
5. The checkers found that a bath of dry ice and acetone worked equally well.
6. A single transfer under high vacuum afforded a product of identical purity. The major contaminants appear to be small amounts of high-boiling starting materials.
7. When a 2-m. polypropylene glycol on firebrick column at 75° is used, the retention volume of methyl isocyanide is 55 cc. of helium. Because of an unknown factor in conditioning the column, it is advisable to perform at least two consecutive analyses.

The checkers employed a 5-ft. 20% Carbowax 20 M (terminated with terephthalic acid) on Chromosorb W (acid washed) column at 60°. Methyl isocyanide showed a retention volume of 300 cc. of helium. Only traces of lower-boiling impurities were observed.

3. Discussion

Methyl isocyanide has been prepared chiefly by minor modifications of the original method of Gautier,[3] which is the alkylation of silver cyanide by an alkyl halide.

4. Merits of the Preparation

The excellent procedures for dehydration of N-alkyl- and N-arylformamides developed by Hertler and Corey[4] and by Ugi and co-workers[5] are unsuccessful with low-molecular-weight isocyanides. This common failure is probably due to poor efficiency in extraction of these very polar substances from water. The present method also has been successfully employed for the preparation of smaller quantities of methyl (50%), ethyl (45%), *s*-butyl (35%) and cyclobutyl (24%) isocyanides.[6] The procedure is less laborious than that reported earlier for ethyl isocyanide.[7] For comments on procedures for the preparation of the higher alkyl isocyanides see p. 300 of this volume and reference [8].

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 300
- Org. Syn. Coll. Vol. 5, 1060
- Org. Syn. Coll. Vol. 6, 232
- Org. Syn. Coll. Vol. 7, 27

References and Notes

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

polypropylene glycol

nitrogen (7727-37-9)

zinc (7440-66-6)

Quinoline (91-22-5)

silver cyanide (506-64-9)

Terephthalic acid (100-21-0)

Ethyl isocyanide (624-79-3)

helium (7440-59-7)

Methyl isocyanide (593-75-9)

N-methylformamide (123-39-7)

methyl isocyanate (624-83-9)

p-Toluenesulfonyl chloride (98-59-9)