



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.

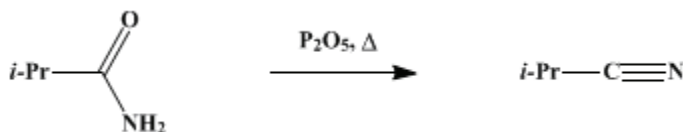
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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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ISOBUTYRONITRILE



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1. Procedure

To 308 g. (2.1 moles) of [phosphorus pentoxide](#) (reagent grade) in a 3-l. round-bottomed flask is added 174 g. (2 moles) of finely powdered, dry [isobutyramide](#) ([Note 1](#)). The flask is tightly stoppered, and the two dry solids are thoroughly mixed by shaking. The flask then is attached to a water-cooled condenser set for downward distillation; a 500-ml. suction flask connected to the condenser by a rubber stopper is a convenient receiver. A calcium chloride tube is attached to the side arm of the receiver, and the receiver is surrounded by crushed ice. The reaction flask is heated for 8–10 hours in an electrically heated oil bath maintained at 200–220°. The nitrile starts to distil almost at once. The reaction mixture becomes a thick, brown syrup which foams considerably toward the end of the distillation. The time of reaction may be cut to 1–2 hours by connecting the distillation system to an aspirator and intermittently removing the nitrile under reduced pressure ([Note 2](#)). Very little additional nitrile can be obtained by further heating of the reaction mixture.

The contents of the receiver are transferred to a 500-ml. modified Claisen flask, 10–15 g. of [phosphorus pentoxide](#) is added ([Note 3](#)), and the product is distilled from an oil bath held at 145–155°. After only a few drops of fore-run, the main fraction distils at 99–102°/740 mm. The yield is 96–120 g. (69–86%). The product is colorless when first distilled but acquires a yellow tint after standing a few days. If it is again distilled from [phosphorus pentoxide](#) or Drierite, it boils at 101–103° and remains colorless; n_D^{25} 1.3713.

2. Notes

1. The amide must be thoroughly dry or immediate reaction will take place with considerable generation of heat, and the yield will be lowered owing to the failure to obtain proper mixing of the reactants. If the amide is not finely powdered the yield of nitrile falls off sharply.
2. The yield is not altered by this procedure if care is taken not to evaporate the nitrile in the receiver. Keeping the flask surrounded by crushed ice and using a Dry Ice-acetone safety trap between the receiver and aspirator will guard against such loss.
3. When [phosphorus pentoxide](#) is added to [isobutyronitrile](#), the liquid sets to a semisolid gel which is difficult to transfer from a flask. Hence, the addition of one to the other should be made only in the flask from which the distillation is to be made.

3. Discussion

[Isobutyronitrile](#) has been prepared by a number of catalytic vapor-phase reactions at elevated temperatures: [isobutylamine](#) over [copper](#)¹ or [nickel](#),² [isobutyramide](#) over [alumina](#),³ a mixture of [ammonia](#) and [isobutyraldehyde](#) over [thorium dioxide](#)⁴ or other catalysts,⁵ a mixture of [ammonia](#) and [isobutyl alcohol](#) over [copper](#),⁶ and a mixture of [isobutylene oxide](#) and [ammonia](#) over [alumina](#) and [copper](#).⁷ It has also been prepared by decarboxylation of [2-methyl-2-cyanopropanoic acid](#),⁸ and by the reaction of [isobutyric acid](#) with [potassium thiocyanate](#).⁹ The above procedure is a modification of the method used by Walter and McElvain.¹⁰

References and Notes

1. Mailhe and de Godon, *J. pharm. chim.*, (7) **16**, 225 (1917) (*Chem. Zentr.*, **1918**, I, 819).
 2. Mailhe and de Godon, *Bull. soc. chim. France*, (4) **21**, 288 (1917).
 3. Boehmer and Andrews, *J. Am. Chem. Soc.*, **38**, 2503 (1916).
 4. Mailhe, *Compt. rend.*, **166**, 215 (1918).
 5. U. S. pat. 2,535,818 [*C. A.*, **45**, 2015 (1951)].
 6. Hara and Komatsu, *Mem. Coll. Sci. Kyoto Imp. Univ.*, **8A**, 241 (1925) [*C. A.*, **19**, 3248 (1925)].
 7. U. S. pat. 2,500,256 [*C. A.*, **44**, 7342 (1950)].
 8. Hoffmann and Barbier, *Bull. soc. chim. Belg.*, **45**, 565 (1936) [*C. A.*, **31**, 919 (1937)].
 9. Letts, *Ber.*, **5**, 671 (1872).
 10. Walter and McElvain, *J. Am. Chem. Soc.*, **56**, 1614 (1934).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

alumina

Drierite

ammonia (7664-41-7)

thorium dioxide

copper (7440-50-8)

nickel (7440-02-0)

potassium thiocyanate (333-20-0)

isobutyl alcohol (78-83-1)

isobutyraldehyde (78-84-2)

Isobutyramide (563-83-7)

isobutyric acid (79-31-2)

Isobutyronitrile (78-82-0)

isobutylamine (78-81-9)

isobutylene oxide (558-30-5)

2-methyl-2-cyanopropanoic acid

phosphorus pentoxide (1314-56-3)