



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.

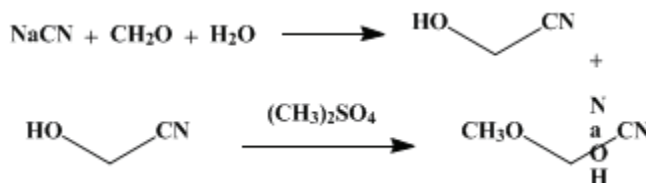
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 2, p.387 (1943); Vol. 13, p.56 (1933).

METHOXYACETONITRILE

[Acetonitrile, methoxy-]



Submitted by J. A. Scarrow and C. F. H. Allen.

Checked by Reynold C. Fuson and Charles F. Woodward.

1. Procedure

This preparation must be carried out in a hood having good suction. Methyl sulfate has a high vapor pressure in spite of its high boiling point and is very poisonous. Ammonia is a specific antidote and should be kept on hand to destroy any of the ester accidentally spilled. It is advisable to wash the hands in dilute ammonium hydroxide frequently.

In a 1-l. three-necked, round-bottomed flask, fitted with a stirrer, a thermometer for reading low temperatures (Note 1), and a dropping funnel, are placed 98 g. (2 moles) of pulverized sodium cyanide (Note 2) and 200 cc. of water. The stirrer is started, and 60 g. of paraformaldehyde (2 moles) (Note 3) is added in small quantities until the temperature rises to 20–25° and the sodium cyanide has dissolved. The flask is then surrounded by a freezing mixture, and the temperature is kept below 25° during the introduction of the remaining paraformaldehyde.

Two hundred cubic centimeters (270 g., 2.1 moles) of technical methyl sulfate is placed in the dropping funnel, and, when the temperature inside the flask has dropped to 13°, a 20- to 30-cc. portion of the sulfate is added. An exothermic reaction should set in; the ice bath is removed, if necessary, to get the reaction to start (Note 4). When the temperature begins to fall, the remainder of the methyl sulfate is admitted at such a rate as to keep the temperature at 12–15°; this takes at least twenty minutes. When the addition is complete the mixture is stirred an additional forty minutes; during this time the temperature will drop to about 5°. The stirrer is stopped, and the oily, upper layer is separated at once (Note 5). The lower, aqueous layer is returned to the flask and methylated as before with a second 200-cc. portion of methyl sulfate (Note 6).

The oily, upper layer is dried with 10 g. of anhydrous sodium sulfate (Note 7) and is distilled under diminished pressure. For this purpose an efficient fractionating column (Note 8) is used. The portion boiling below 70° at 15 mm. is mainly methoxyacetonitrile and weighs 60–70 g. The upper layer from the second methylation is treated in a similar manner; the distillate weighs 55–60 g. The residue in the distilling flask is methyl sulfate and is used in a subsequent run (Note 9).

The crude fractions are combined and distilled at atmospheric pressure through a good column; about 95 per cent distills at 118–122° as a colorless liquid. The methoxyacetonitrile so prepared weighs 100–110 g. (70–77 per cent of the theoretical amount).

2. Notes

1. A 30- to 35-cm. thermometer reading from –50 to +50° is most convenient since the graduations used are then outside the flask.
2. Potassium cyanide gives poorer results.
3. An equivalent amount of commercial formalin solution can be used with equally good results, provided that allowance is made for the volume of water—the total volume must not exceed 200 cc.
4. The reaction usually starts immediately; occasionally it does not start until the mixture becomes

warm.

5. If the mixture is allowed to stand, the temperature rises to 40–50°, a red color develops, and the yield drops to almost nothing.

6. Recovered [methyl sulfate](#) can be used without purification.

7. No drying agent is completely satisfactory; [sodium sulfate](#) does the least harm.

8. The authors found a Glinsky column most satisfactory. A capillary tube reaching to the bottom of the flask for the admission of air is essential to prevent bumping. In the redistillation a piece of porous plate is sufficient for this purpose.

9. The density of the residual liquid in two runs was found to be 1.31, 1.32. The pure ester has a density of 1.35.

3. Discussion

[Methoxyacetonitrile](#) has been prepared by methylating [hydroxyacetonitrile](#) with [methyl sulfate](#);¹ by treating [chloromethyl ether](#) with cuprous or mercuric cyanide;² and by dehydrating [methoxyacetamide](#) with [phosphorus pentoxide](#).³ The procedure described is a modification of that of Polstorff and Meyer.¹

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 3, 562](#)

References and Notes

1. Polstorff and Meyer, *Ber.* **45**, 1911 (1912); Slater and Stephen, *J. Chem. Soc.* **117**, 312 (1920); Malkin and Robinson, *ibid.* **127**, 372 (1925).
2. Gauthier, *Ann. chim. phys.* (8) **16**, 302, 306 (1909).
3. Kilpi, *Z. physik. Chem.* **86**, 671 (1914).

Appendix

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

cuprous or mercuric cyanide

[ammonia](#) (7664-41-7)

[formalin](#) (50-00-0)

[sodium cyanide](#) (143-33-9)

[sodium sulfate](#) (7757-82-6)

[potassium cyanide](#) (151-50-8)

[sulfate](#) (14808-79-8)

[ammonium hydroxide](#) (1336-21-6)

[methyl sulfate](#) (75-93-4)

chloromethyl ether (542-88-1)

Methoxyacetonitrile,
Acetonitrile, methoxy- (1738-36-9)

hydroxyacetonitrile (107-16-4)

methoxyacetamide (16332-06-2)

phosphorus pentoxide (1314-56-3)

paraformaldehyde (30525-89-4)