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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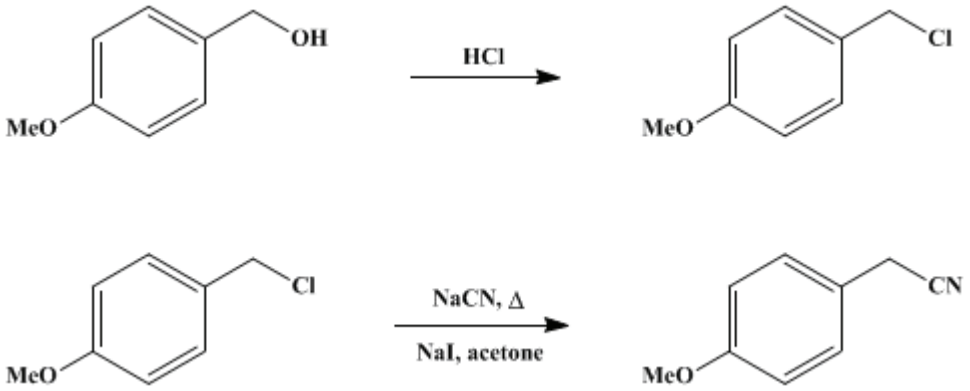
p-METHOXYPHENYLACETONITRILE

[Acetonitrile, *p*-methoxyphenyl-]



Submitted by Kurt Rorig, J. Derland Johnston, Robert W. Hamilton, and Thomas J. Telinski[1].
Checked by William S. Johnson, Stanley Seltzer, and Peter Yates.

1. Procedure

In a 1-l. flask fitted with a paddle-blade stirrer are placed 138 g. (1 mole) of anisyl alcohol (Note 1) and 248 ml. of concentrated hydrochloric acid. After stirring vigorously for 15 minutes the contents of the flask are transferred to a separatory funnel. The lower layer (anisyl chloride) is separated, dried over 20 g. of granular calcium chloride for about 30 minutes, and filtered to remove the drying agent.

In a 2-l. three-necked round-bottomed flask, fitted with an efficient sealed stirrer and a reflux condenser capped by a drying tube, are placed the dried anisyl chloride (Note 2) and (Note 3), 73.6 g. (1.5 moles) of finely powdered sodium cyanide, 10 g. of sodium iodide, and 500 ml. of dry acetone (Note 4). The heterogeneous reaction mixture is heated under reflux with vigorous stirring for 16–20 hours, then cooled and filtered with suction. The solid on the filter is washed with 200 ml. of acetone and discarded (Note 5). The combined filtrates are distilled to remove the acetone. The residual oil is taken up in 300 ml. of benzene and washed with three 100-ml. portions of hot water. The benzene solution is dried over anhydrous sodium sulfate for about 15 minutes, and the solvent is removed by distillation at the reduced pressure of the water aspirator (Note 6). The residual *p*-methoxyphenylacetonitrile is purified by distillation under reduced pressure through an 8-in. Vigreux column; b.p. 94–97°/0.3 mm.; n_D^{25} 1.5285–1.5291. The yield is 109–119 g., or 74–81% based on anisyl alcohol (Note 7) and (Note 8).

2. Notes

1. Givaudan-Delawanna (330 W. 42nd Street, New York 18, N. Y.) "Anisic Alcohol" of 97% minimum purity was used.
2. The crude anisyl chloride is unstable. It should be used the same day it is made.
3. This step should be performed in a well-ventilated hood.
4. The acetone is dried over about one-quarter its volume of granular calcium chloride for one day. The dried acetone is then filtered and distilled.
5. This residue should be discarded with due regard for the unused sodium cyanide it contains.
6. The undistilled *p*-methoxyphenylacetonitrile weighs 125–139 g. (85–95%) and has a refractive index close to that of the distilled product. It can be used for many purposes, such as condensation with aromatic aldehydes to yield α-*p*-methoxyphenylcinnamonitriles, without further purification.
7. The submitters have carried out this preparation on five times the scale described here with comparable yields.
8. This method is particularly applicable to the more reactive benzyl halides which are easily

hydrolyzed in the aqueous media usually employed for the metathetical reaction with alkali cyanides. For example, anisyl chloride treated with sodium cyanide in aqueous dioxane gives, as a by-product, 5–10% of anisyl alcohol as determined by infrared analysis. The use of anhydrous acetone not only prevents hydrolysis to the alcohol but also decreases the formation of isonitriles. This method was also applied successfully by the submitters to the preparation of *p*-chlorophenylacetonitrile in 74% yield.

3. Discussion

This method is an adaptation of that of Dengel.[2] *p*-Methoxyphenylacetonitrile can also be prepared by the metathetical reaction of anisyl chloride with alkali cyanides in a variety of aqueous solvent mixtures;[3,4,5,6,7,8,9,10,11] by the nitration of phenylacetonitrile, followed by reduction, diazotization, hydrolysis, and methylation;[12,13] by the reduction of α-benzoxy-*p*-methoxyphenylacetonitrile (prepared from anisaldehyde, sodium cyanide, and benzoyl chloride);[14] by the reaction of acetic anhydride with the oxime of *p*-methoxyphenylpyruvic acid;[15] and through the condensation of *p*-methoxybenzaldehyde with rhodanine.[16]

References and Notes

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

oxime of p-methoxyphenylpyruvic acid

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium cyanide (143-33-9)

sodium sulfate (7757-82-6)

acetone (67-64-1)

benzoyl chloride (98-88-4)

phenylacetonitrile (140-29-4)

Anisic Alcohol (90-05-1)

sodium iodide (7681-82-5)

dioxane (123-91-1)

Rhodanine (141-84-4)

p-chlorophenylacetonitrile (140-53-4)

anisyl alcohol (150-76-5)

anisyl chloride (623-12-1)

anisaldehyde,
p-methoxybenzaldehyde (123-11-5)

p-Methoxyphenylacetonitrile,
Acetonitrile, p-methoxyphenyl- (104-47-2)

α-benzoxy-p-methoxyphenylacetonitrile