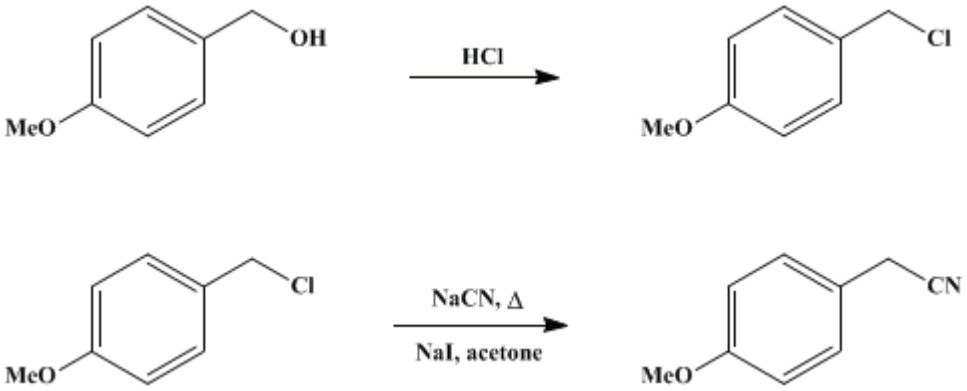
Organic Syntheses, Coll. Vol. 4, p.576 (1963); Vol. 36, p.50 (1956).

p-METHOXYPHENYLACETONITRILE

[Acetonitrile, *p*-methoxyphenyl-]



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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

1. G. D. Searle and Company, Chicago 80, Illinois.
2. Dengel, German pat. application (DBP, Anm. K2355, March 30, 1950; Knoll-A.G.) as reported by Müller, *Methoden der Organischen Chemie* (Houben-Weyl), Vol. 8, p. 294, Georg Thieme Verlag, Stuttgart, 1952.
3. Shriner and Hull, *J. Org. Chem.*, **10**, 230 (1945).
4. Métayer, *Ann. chim. Paris*, [12] **4**, 210 (1949).
5. Van Heyningen, *J. Am. Chem. Soc.*, **74**, 4862 (1952).
6. Dankova, Evdokimova, Stepanov, and Preobrazhenskii, *Zhur. Obshchei Khim.*, **18**, 1724 (1948) [*C. A.*, **43**, 2606 (1949)].
7. Lapiné, *Bull. soc. chim. France*, [5] **6**, 390 (1939).
8. Lee, Ziering, Berger, and Heineman, *Jubilee Vol. Emil Barell*, **1946**, 280 [*C. A.*, **41**, 6252 (1947)].
9. Livshits, Bazilevskaya, Bainova, Dobrovinskaya, and Preobrazhenskii, *Zhur. Obshchei Khim.*, **17**, 1675 (1947) [*C. A.*, **42**, 2606 (1948)].
10. Cagniant, *Ann. chim. (Paris)*, **7**, 442 (1952).
11. Burckhalter, Jackson, Sam, and Meyer, *J. Am. Chem. Soc.*, **76**, 4112 (1954).
12. Pschorr, Wolfes, and Buckow, *Ber.*, **33**, 171 (1900).
13. Silverman and Bogert, *J. Org. Chem.*, **11**, 43 (1946).
14. Campbell and McKail, *J. Chem. Soc.*, **1948**, 1255; Wawzonek and Fredrickson, *J. Electrochem. Soc.*, **106**, 325 (1959).
15. Baker and Eastwood, *J. Chem. Soc.*, **1929**, 2902; Seshadri and Varadarajan, *Proc. Indian Acad. Sci.*, **37A**, 145 (1953).
16. Yoder, Cheng, and Burroughs, *Proc. Iowa Acad. Sci.*, **61**, 271 (1954) [*C. A.*, **49**, 13236 (1955)].

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 (5703-46-8)

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