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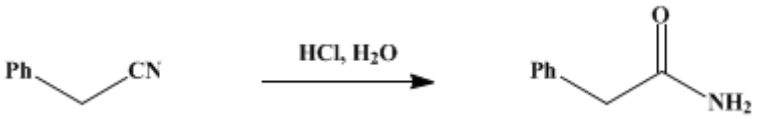
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.032.0092

Organic Syntheses, Coll. Vol. 4, p.760 (1963); Vol. 32, p.92 (1952).

PHENYLACETAMIDE

[Acetamide, 2-phenyl-]



Submitted by Wilhelm Wenner[1]
Checked by William S. Johnson and Robert E. Ireland.

1. Procedure

In a 3-l. three-necked round-bottomed flask equipped with glass joints are placed 200 g. (1.71 moles) of benzyl cyanide (Note 1) and 800 ml. of 35% hydrochloric acid (Note 2). The flask is fitted with a reflux condenser, a thermometer, and an efficient mechanical stirrer (Note 3). At a bath temperature of about 40° (Note 4) the mixture is stirred vigorously. Within a period of 20–40 minutes the benzyl cyanide goes into solution (Note 3). During this time, the temperature of the reaction mixture rises about 10° above that of the bath. The homogeneous solution is kept in the bath with, or without, stirring for an additional 20–30 minutes (Note 5). The warm water in the bath is replaced by tap water at about 15–20°, and the thermometer is replaced by a dropping funnel from which 800 ml. of cold distilled water is added with stirring (Note 6). After the addition of about 100–150 ml., crystals begin to separate. When the total amount of water has been added, the mixture is cooled externally with ice water for about 30 minutes (Note 7). The cooled mixture is filtered by suction. Crude phenylacetamide remains on the filter and is washed with two 100-ml. portions of water. The crystals are then dried at 50–80°. The yield of crude phenylacetamide is 190–200 g. (82–86%). It is sufficiently pure for most purposes although it contains traces of phenylacetic acid. If pure phenylacetamide is desired, the crude, wet solid is stirred for about 30 minutes with 500 ml. of a 10% solution of sodium carbonate, collected on a suction funnel, washed with two 100-ml. portions of cold water, and dried. The yield of this product is 180–190 g. (78–82%); m.p. 154–155° (Note 8) and (Note 9).

2. Notes

1. The quality of the benzyl cyanide markedly affects the yields. Material prepared according to directions given previously[2] is satisfactory. Several commercially available grades were also found to be usable without distillation.
2. The hydrochloric acid must be of at least 30% strength.
3. Efficient stirring is of prime importance for satisfactory reaction, because intimate mixing of the heterogeneous mixture is necessary. The rate of dissolution of the nitrile depends on the efficiency of the stirring.
4. The reaction proceeds slowly at lower temperatures. Temperatures above 50° are not recommended because of the high volatility of hydrochloric acid.
5. This additional warming ensures complete reaction of some dissolved benzyl cyanide. The phenylacetamide is not readily hydrolyzed under these conditions.
6. The rate of addition is not critical.
7. If phenylacetic acid is desired, the suspension of phenylacetamide is refluxed with stirring and the phenylacetamide redissolves. After about 30 minutes, the mixture becomes turbid and the product begins to separate as an oil. After 6 hours the mixture is cooled, first with tap water and then by an ice-water bath. When the temperature has dropped to about 40–50°, the phenylacetic acid crystallizes. After cooling at 0° for about 4 hours (the acid is rather soluble in warm water), the mixture is filtered by suction. The crude, colorless phenylacetic acid is washed with two 100-ml. portions of cold water and dried in a desiccator. The yield of crude acid is 180–195 g. (77.5–84%). It melts at 66–70° and is sufficiently pure for most purposes. The mother liquor on extraction with two 150-ml. portions of benzene and evaporation yields an additional 3–5 g. of acid. To prepare the pure acid, vacuum

distillation (as described by Adams and Thal[3]) is simpler and gives higher yields than recrystallization from ligroin.
8. Further purification is effected by recrystallization from 95% ethanol or benzene, yielding the pure compound of m.p. 156°.
9. The following arylacetamides have been prepared from the corresponding nitriles by the same method in the indicated yields:[4] *p*-methylphenylacetamide (70%), *p*-isopropylphenylacetamide (90%), 1-naphthylacetamide (54%), 5,6,7,8-tetrahydro-2-naphthylacetamide (90%), *p*-methoxyphenylacetamide (76%), 3,4-dimethoxyphenylacetamide (82%), and 2,3-dimethoxyphenylacetamide (91%). Only in the cases of the alkoxy-substituted nitriles are the resulting amides soluble in the reaction mixture; the other nitriles do not dissolve completely at any time during the reaction.

3. Discussion

Phenylacetamide has been obtained by a wide variety of reactions: from benzyl cyanide with water at 250–260°;[5] from benzyl cyanide with water and cadmium oxide at 240°;[6] from benzyl cyanide with sulfuric acid;[7,8] by saturation of an acetone solution of benzyl cyanide with potassium hydrosulfide;[9] from benzyl cyanide with sodium peroxide;[10] by electrolytic reduction of benzyl cyanide in sodium hydroxide;[11] from ethyl phenylacetate with alcoholic[12] or aqueous[13] ammonia; from phenylacetic acid with ammonium acetate[14] or urea;[15] from diazoacetophenone with ammoniacal silver solution;[16] from phenylacetic acid imino ether hydrochloride and water;[17] from acetophenone with ammonium polysulfide;[18] from benzoic acid;[19] by heating the ammonium salt of phenylacetic acid;[20] and by heating cinnamic acid with a mixture of sulfur and ammonium hydroxide.[21]

The literature on the preparation of phenylacetic acid is reviewed in an earlier volume of this series.[3]

The present method is that of Wenner[22] and is applicable to other arylacetonitriles.[4]

References and Notes

1. Hoffmann-La Roche, Inc., Nutley, New Jersey.
2. *Org. Syntheses Coll. Vol.* **1**, 107 (1941).
3. *Org. Syntheses Coll. Vol.* **1**, 436 (1941).
4. Wenner, *J. Org. Chem.*, **15**, 548 (1950).
5. Bernthsen, *Ann.*, **184**, 318 (1877).
6. I. G. Farbenind., Ger. pat. 551,869 [*C. A.*, **26**, 4826 (1932)].
7. Maxwell, *Ber.*, **12**, 1764 (1879).
8. Purgotti, *Gazz. chim. ital.*, **20**, 173, 593 (1891).
9. Weddige, *J. prakt. Chem.*, [2] **7**, 99 (1873).
10. Deinert, *J. prakt. Chem.*, [2] **52**, 432 (1895).
11. Ogura, *Mem. Coll. Sci., Kyoto Imp. Univ.*, **12A**, 339 (1929) [*C. A.*, **24**, 2060 (1930)].
12. Fischer and Dilthey, *Ber.*, **35**, 856 (1902).
13. Meyer, *Monatsh.*, **27**, 34 (1906).
14. Kao and Ma, *J. Chem. Soc.*, **1930**, 2788; **1931**, 443.
15. Das-Gupta, *J. Ind. Chem. Soc.*, **10**, 117 (1933).
16. Wolff, *Ann.*, **394**, 43 (1912).
17. Houben, *Ber.*, **59**, 2878 (1926).
18. Willgerodt and Scholtz, *J. prakt. Chem.*, [2] **81**, 384 (1910); British Petroleum Ltd., Brit. pat. 772,443 [*C. A.*, **51**, 14811 (1957)]; Shchukina and Golombik, *Med. Prom. S.S.S.R.*, **11**, No. 7, 42 (1957) [*C. A.*, **52**, 10943 (1958)]; DeTar and Carmack, *J. Am. Chem. Soc.*, **68**, 2025 (1946); Carmack and DeTar, *J. Am. Chem. Soc.*, **68**, 2029 (1946); Pattison and Carmack, *J. Am. Chem. Soc.*, **68**, 2033 (1946).
19. Arndt and Eistert, *Ber.*, **68**, 200 (1935).
20. Menschutkin, *Ber.*, **31**, 1429 (1898).
21. Davis and Carmack, *J. Org. Chem.*, **12**, 76 (1947).
22. Wenner, U. S. pat. 2,489,348 [*C. A.*, **44**, 2559 (1950)].

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

ligroin

ammonium polysulfide

ammoniacal silver

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ammonium acetate (631-61-8)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

Benzoic acid (65-85-0)

sulfur (7704-34-9)

acetone solution of benzyl cyanide (67-64-1)

Acetophenone (98-86-2)

Benzyl cyanide (140-29-4)

Phenylacetic acid (103-82-2)

urea (57-13-6)

sodium peroxide

ammonium hydroxide (1336-21-6)

potassium hydrosulfide (1310-61-8)

cinnamic acid (621-82-9)

Ethyl phenylacetate (101-97-3)

cadmium oxide

Phenylacetamide,
Acetamide, 2-phenyl- (103-81-1)

1-naphthylacetamide (86-86-2)

5,6,7,8-tetrahydro-2-naphthylacetamide

3,4-dimethoxyphenylacetamide

2,3-dimethoxyphenylacetamide

Diazoacetophenone (3282-32-4)

phenylacetic acid imino ether hydrochloride

p-methylphenylacetamide

p-isopropylphenylacetamide

p-methoxyphenylacetamide (6343-93-7)

ammonium salt of phenylacetic acid