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.

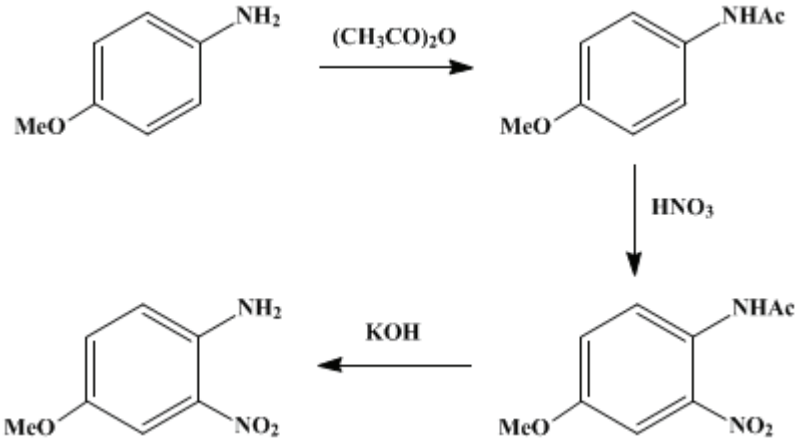
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.025.0078

Organic Syntheses, Coll. Vol. 3, p.661 (1955); Vol. 25, p.78 (1945).

2-NITRO-4-METHOXYANILINE

[*p*-Anisidine, 2-nitro-]



Submitted by Paul E. Fanta and D. S. Tarbell.
Checked by W. E. Bachmann and N. C. Deno.

1. Procedure

A. *2-Nitro-4-methoxyacetanilide.* In a 2-l. three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermometer are placed 123 g. (1 mole) of *p*-anisidine (Note 1), 300 ml. of glacial acetic acid, and 217 ml. of water. Stirring is started, and, when the *p*-anisidine has dissolved, 350 g. of ice is added. When the temperature reaches 0–5°, 103 ml. (1.1 moles) of acetic anhydride is added all at once with rapid stirring. Within several seconds the contents of the flask set to a crystalline mass and the temperature rises to 20–25°. The flask is heated on a steam bath until the crystalline material dissolves and is then cooled with stirring to 45°, at which temperature crystals begin to separate. An ice bath is applied, and 100 ml. (55% excess) of concentrated nitric acid (sp. gr. 1.42) is added all at once. The temperature rises rapidly to 70° and soon begins to fall. By suitable adjustment of the cooling bath the temperature is maintained at 60–65° for 10 minutes and then brought down to 25° in the course of 10 minutes (Note 2).

The solution is chilled overnight in an ice chest, and the precipitated yellow crystals are collected on a 19-cm. Büchner funnel. The crystals are washed with 270 ml. of ice-cold water and pressed as dry as possible with a rubber dam. The filter cake can be dried (Note 3) in air or in a vacuum desiccator over calcium chloride and soda lime. The yield of 2-nitro-4-methoxyacetanilide melting at 116–116.5° is 158–168 g. (75–79%).

B. 2-*Nitro*-4-*methoxyaniline.* A mixture of 160 g. of 2-nitro-4-methoxyacetanilide and 250 ml. of cold Claisen's alkali (Note 4) in a 2-l. beaker is stirred and warmed on a steam bath for 15 minutes; it first becomes liquid and then sets to a thick, red paste. After the addition of 250 ml. of hot water the mixture is stirred and digested on a steam bath for an additional 15 minutes and then cooled to 0–5°. The product is collected on a 19-cm. Büchner funnel, washed with three 160-ml. portions of ice-cold water, and pressed as dry as possible with a rubber dam. The yield of vacuum-dried product melting at 122.5–123° is 122–124 g. (95–97%).

2. Notes

1. Eastman Kodak Company's Practical grade of *p*-anisidine was used.
2. In a run in which the mixture was allowed to cool spontaneously from 65° the product became dark.
3. Drying is unnecessary if the 2-nitro-4-methoxyacetanilide is used in step B. The material may be

recrystallized with 97% recovery from dilute aqueous ethanol (2 ml. of 95% ethanol and 4 ml. of water per gram). The product so obtained melts at 116.5–117°.
4. Claisen's alkali is prepared by dissolving 88 g. of potassium hydroxide in 63 ml. of water, cooling, and diluting to 250 ml. with methanol.

3. Discussion

2-Nitro-4-methoxyacetanilide has been prepared by the nitration of *p*-acetaniside.[1] [2] [3] [4] The procedure described for the nitration is essentially that used by Lothrop.[4]

2-Nitro-4-methoxyaniline has been prepared by heating nitrohydroquinone dimethyl ether with aqueous ammonia;[5] by heating the tetramethylammonium salt of 3-nitro-4-aminophenol;[6] by the hydrolysis of 2-nitro-4-methoxyacetanilide[1] with alcoholic potassium hydroxide[2,3] or hydrochloric acid;[4] and by the hydrolysis of the *p*-toluenesulfonamide,[7] the 3-nitrobenzenesulfonamide,[8] the 3-nitro-*p*-toluenesulfonamide,[8] the benzenesulfonamide,[9] and the acetyl derivative of the *p*-toluenesulfonamide[10] of 2-nitro-4-methoxyaniline with concentrated sulfuric acid.

References and Notes

1. Hinsberg, *Ann.*, **292**, 249 (1896);
2. Reverdin, *Ber.*, **29**, 2595 (1896); *Jahresb.*, **1896**, 1156; *Bull. soc. chim. France*, (3) **17**, 115 (1897);
3. Hata, Tatematsu, and Kubota, *Bull. Chem. Soc. Japan*, **10**, 425 (1935) [*C. A.*, **30**, 1056 (1936)];
4. Lothrop, *J. Am. Chem. Soc.*, **64**, 1698 (1942).
5. Scheidel, Ger. pat. 36,014 [*Frdl.*, **1**, 221 (1888)].
6. Hahle, *J. prakt. Chem.*, (2) **43**, 66 (1891).
7. Reverdin, *Ber.*, **42**, 1525 (1909); Simonov, *J. Gen. Chem. U.S.S.R.*, **10**, 1580 (1940) [*C. A.*, **35**, 2870 (1941)].
8. Reverdin and de Luc, *Ber.*, **45**, 352 (1912).
9. Elderfield, Gensler, and Birstein, *J. Org. Chem.*, **11**, 812 (1946).
10. Reverdin and de Luc, *Ber.*, **43**, 3461 (1910).

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

soda lime

Nitro-4-methoxyacetanilide

2-Nitro-4-methoxyacetanilide

acetyl derivative of the p-toluenesulfonamide

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

potassium hydroxide (1310-58-3)

2-Nitro-4-methoxyaniline,
p-Anisidine, 2-nitro- (96-96-8)

Benzenesulfonamide (98-10-2)

nitrohydroquinone dimethyl ether (89-39-4)

3-nitrobenzenesulfonamide (121-52-8)

p-anisidine (104-94-9)

p-toluenesulfonamide (70-55-3)

p-acetaniside (51-66-1)

3-nitro-p-toluenesulfonamide

tetramethylammonium salt of 3-nitro-4-aminophenol