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.

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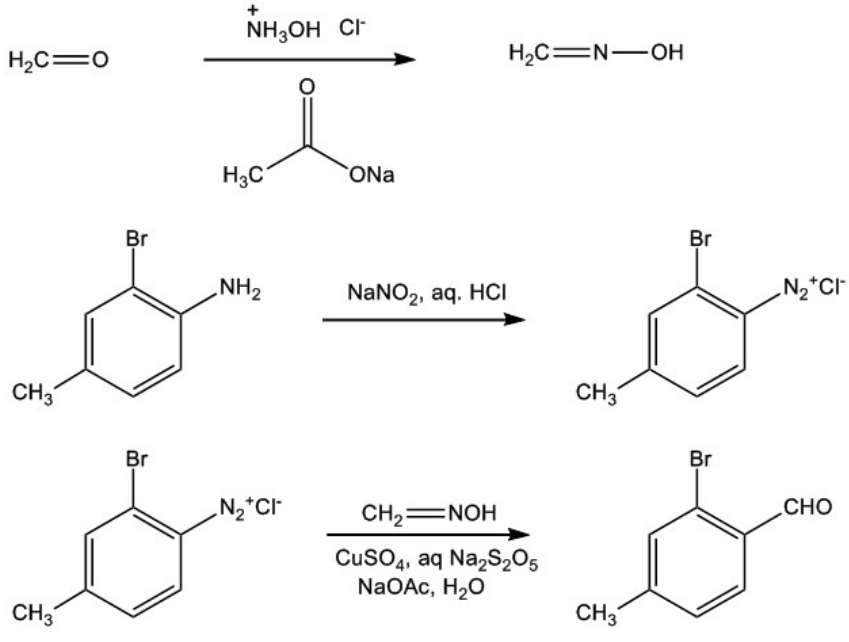
2-BROMO-4-METHYLBENZALDEHYDE

[*p*-Tolualdehyde, 2-bromo-]



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Checked by A. G. Szabo and Peter Yates.

1. Procedure

CAUTION! The procedures in this article should be performed in a fume hood and researchers should take appropriate precautions due to the possibility of the generation of HCN as a side product during the reaction and isolation procedures. [Note added April 2017].

A. *Formaldoxime*. A mixture of 11.5 g. (0.38 mole) of paraformaldehyde and 26.3 g. (0.38 mole) of hydroxylamine hydrochloride in 170 ml. of water is heated until a clear solution is obtained. Then there is added 51 g. (0.38 mole) of hydrated sodium acetate, and the mixture is boiled gently under reflux for 15 minutes to give a 10% solution of formaldoxime.

B. *2-Bromo-4-methylbenzenediazonium chloride*. A mixture of 46.0 g. (0.25 mole) of 2-bromo-4-methylaniline[2] and 50 ml. of water is placed in a 1-l. three-necked flask equipped with an efficient stirrer, a dropping funnel, and a thermometer. The stirrer is started, and 57 ml. of concentrated hydrochloric acid is added slowly. The mixture is cooled to room temperature, 100 g. of ice is added, and the temperature of the mixture is maintained at −5° to +5° by means of an ice-salt bath. To the stirred mixture there is added, dropwise, a solution of 17.5 g. (0.25 mole) of sodium nitrite in 25 ml. of water. After completion of the addition, the stirring is continued for a period of 15 minutes. The stirred solution of the diazonium salt is made neutral to Congo red by the addition of a solution of hydrated sodium acetate (22 g.) in water (35 ml.) (Note 1).

C. *2-Bromo-4-methylbenzaldehyde*. A 3-l. three-necked flask is equipped with an efficient stirrer, a dropping funnel (Note 2), and a thermometer. The aqueous 10% formaldoxime prepared in step A is placed in the flask, and to it are added 6.5 g. (0.026 mole) of hydrated cupric sulfate, 1.0 g. (0.0079 mole) of sodium sulfite, and a solution of 160 g. of hydrated sodium acetate in 180 ml. of water. The solution is maintained at 10–15° by means of a cold-water bath and stirred vigorously. The neutral diazonium salt solution prepared in step B is slowly introduced below the surface of the formaldoxime solution (Note 3) and (Note 4). After the addition of the diazonium salt solution is complete, the stirring is continued for an additional hour and then the mixture is treated with 230 ml. of concentrated

hydrochloric acid. The stirrer and the dropping funnel are replaced by stoppers, and the mixture is gently heated under reflux for 2 hours. The flask is set up for steam distillation, and the reaction product is steam-distilled. The distillate is saturated with sodium chloride, extracted with three 150-ml. portions of ether, and the ethereal extracts are washed successively with three 20-ml. portions of a saturated sodium chloride solution, three 20-ml. portions of an aqueous 10% sodium bicarbonate solution, and again with three 20-ml. portions of a saturated sodium chloride solution.

The ether is distilled and to the residue there is added, with cooling, 90 ml. of an aqueous 40% sodium metabisulfite solution, previously heated to 60°. The mixture is shaken for 1 hour and allowed to stand overnight. The solid addition product is filtered, washed twice with ether, and then suspended in 200 ml. of water in a 500-ml. flask, and 40 ml. of concentrated sulfuric acid is slowly added with cooling. The mixture is gently boiled under reflux for 2 hours, cooled, and extracted with three 100-ml. portions of ether. The ethereal extract is washed with three 15-ml. portions of a saturated sodium chloride solution and dried over anhydrous sodium sulfate. The ether is evaporated, and the product is distilled under reduced pressure. 2-Bromo-4-methylbenzaldehyde distills at 114–115° (5 mm.) as a colorless oil, yield 17.5–22.5 g. (35–45%), which crystallizes in the receiver, m.p. 30–31°.

2. Notes

1. Exact neutralization of the diazonium salt solution is necessary in order to minimize coupling.
2. The stem of the dropping funnel should extend a little below the surface of the solution in the three-necked flask.
3. Addition of the diazonium salt solution sometimes results in the formation of a pasty mass which prevents further stirring; the mixture is then allowed to stand for a further period of 1 hour.
4. The checkers found it preferable to transfer the diazonium salt solution by siphoning under slight nitrogen pressure.

3. Discussion

The preparation of this aldehyde is based on the reaction due to Beech[3] for the conversion of an aromatic amine to the corresponding aldehyde and has been described earlier by Jolad and Rajagopal.[4]

4. Merits of the Preparation

This method of preparation of a halobenzaldehyde is of wide application and has been used for the preparation of the following substituted benzaldehydes: 2-bromo-5-methyl-,[4] 2,3-dichloro- and 2,4-dichloro-,[5] 2-chloro-4-methyl-,[6] 2-methyl-4-bromo- and 3-methyl-4-bromo-,[7] 2-methyl-5-chloro- and 2-methyl-5-bromo-,[8] *p*-iodo-, *p*-fluoro-, 2-iodo-4-methyl-, and 6-iodo-3-methyl-.[9]

References and Notes

1. Department of Chemistry, Karnatak University, Dharwar, S. India.
2. J. R. Johnson and L. T. Sandborn, *Org. Syntheses*, Coll. Vol. **1**, 111 (1951).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

sodium metabisulfite

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium acetate (127-09-3)

sodium sulfite (7757-83-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

cupric sulfate (7758-98-7)

sodium nitrite (7632-00-0)

2-bromo-4-methylaniline (583-68-6)

Hydroxylamine hydrochloride (5470-11-1)

formaldoxime (75-17-2)

2-Bromo-4-methylbenzaldehyde,
p-Tolualdehyde, 2-bromo- (824-54-4)

2-Bromo-4-methylbenzenediazonium chloride

paraformaldehyde (30525-89-4)