



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.

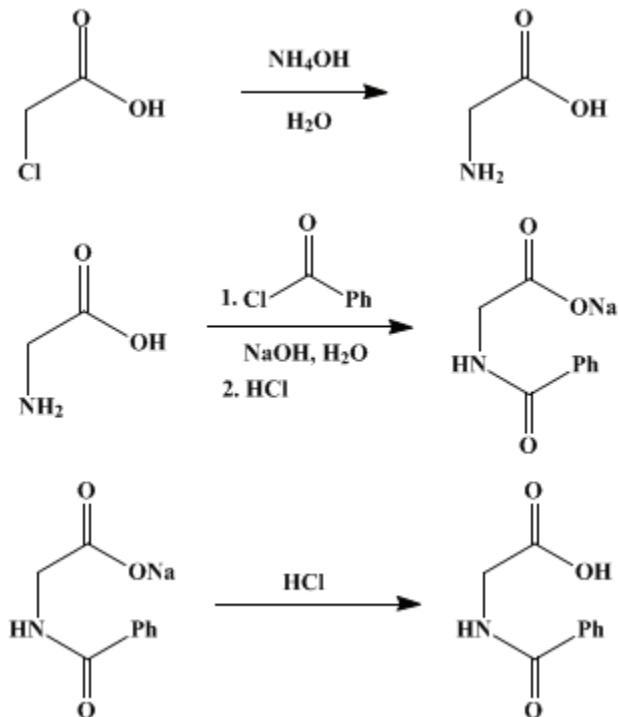
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

Organic Syntheses, Coll. Vol. 2, p.328 (1943); Vol. 12, p.40 (1932).

HIPPURIC ACID



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1. Procedure

To 3 l. (approximately 45 moles) of concentrated ammonium hydroxide (sp. gr. 0.9) (Note 1) in a 5-l. round-bottomed flask is added, with shaking, a solution of 95 g. (1 mole) of chloroacetic acid (Note 2) in 100 cc. of water. The flask is stoppered and allowed to stand for four days (Note 3). It is then attached to a condenser for distillation, and the solution is concentrated to 600–700 cc. The excess ammonia is recovered during this process by connecting the lower end of the condenser to a wide tube leading to the bottom of a 3-l. bottle containing 1.5 l. of distilled water and connecting this in the same way with a smaller bottle containing a little water. The bottles are cooled by running water. About 2 l. of 20–23 per cent ammonium hydroxide is recovered in the first receiver (Note 1).

The residual solution is then transferred to a 2-l. beaker, a solution of 50 g. (1.25 moles) of sodium hydroxide in 100 cc. of water and a little decolorizing carbon are added, and the mixture is boiled until the odor of ammonia is completely absent (Note 4). The solution is filtered by suction, diluted to 500 cc. with water, and transferred to a 2-l. round-bottomed flask equipped with a mechanical stirrer and cooled by running water. While stirring and cooling below 30° , 150 g. (1.1 moles) of benzoyl chloride (Note 2) and a cold solution of 80 g. (2 moles) of sodium hydroxide in 200 cc. of water are admitted separately from separatory funnels at such rates that the solution is always only slightly alkaline. About an hour is required for adding the reagents, and the mixture is stirred for a half hour longer. It is then poured into 125 cc. of concentrated hydrochloric acid in a 2-l. beaker, and, after cooling, the precipitate is filtered and dried. The weight at this point is 150–160 g. The solid is placed in a beaker with 300 cc. of technical carbon tetrachloride, the beaker is covered with a watch glass, and the mixture is boiled gently for ten minutes. The mixture is then cooled slightly, filtered by gentle suction, and the hippuric acid washed on the filter with 50 cc. of carbon tetrachloride (Note 5). After drying, it weighs 135–140 g. For final purification the acid is dissolved in about 2 l. of boiling water, filtered through a steam-heated funnel and allowed to crystallize without artificial cooling. It then appears in characteristic white

needles melting at 186–187°. The yield is 115–122 g. (64–68 per cent of the theoretical amount based on the [chloroacetic acid](#) used). Upon concentrating the mother liquor to 200 cc., a further 6–7 g. of slightly brown [hippuric acid](#) is obtained.

2. Notes

1. An equivalent amount of recovered [ammonium hydroxide](#) (sp. gr. 0.93 or less) was used in a number of runs without reducing the yield.
2. Eastman's "practical" grade reagents were used.
3. The yield was slightly less after two days and no greater after a week.
4. [Ammonia](#) must be completely removed to avoid the formation of [benzamide](#).
5. [Carbon tetrachloride](#) may be recovered by making the filtrate and washings slightly alkaline with [sodium hydroxide](#), refluxing for a half hour to destroy any [benzoyl chloride](#), and then distilling with steam. [Benzoic acid](#) may be recovered by filtering the aqueous residue and acidifying.

3. Discussion

[Hippuric acid](#) has been prepared from the urine of herbivorous animals;¹ by heating [benzamide](#) with [chloroacetic acid](#);² by heating [benzoic anhydride](#) and [glycine](#);³ by heating [benzoic acid](#) and [glycine](#);⁴ by heating [benzoyl chloride](#) with [silver glycinate](#) suspended in [benzene](#),⁵ or with [glycine](#) and [zinc oxide](#);⁶ and by the action of [benzoyl chloride](#) upon an alkaline solution of [glycine](#).⁷

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 2, 55](#)
- [Org. Syn. Coll. Vol. 2, 489](#)

References and Notes

1. Gregory, *Ann.* **63**, 125 (1847); Hallowachs, *ibid.* **106**, 164 (1858); Henneberg, Stohmann, and Rautenberg, *ibid.* **124**, 200 (1862).
 2. Jazukowitsch, *Zeit. für Chem.* **1867**, 466.
 3. Curtius, *Ber.* **17**, 1662 (1884).
 4. Dessaignes, *Jahresb.* **1857**, 367.
 5. Curtius, *J. prakt. Chem.* (2) **26**, 145 (1883).
 6. Dessaignes, *Ann.* **87**, 325 (1853).
 7. Baum, *Ber.* **19**, 502 (1886); *Z. physiol. Chem.* **9**, 465 (1885).
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Appendix

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

[hydrochloric acid](#) (7647-01-0)

[ammonia](#) (7664-41-7)

[Benzene](#) (71-43-2)

[sodium hydroxide](#) (1310-73-2)

[carbon tetrachloride](#) (56-23-5)

Benzoic acid (65-85-0)

chloroacetic acid (79-11-8)

decolorizing carbon (7782-42-5)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

benzamide (55-21-0)

ammonium hydroxide (1336-21-6)

Glycine (513-29-1)

Hippuric acid (495-69-2)

zinc oxide

silver glycinate