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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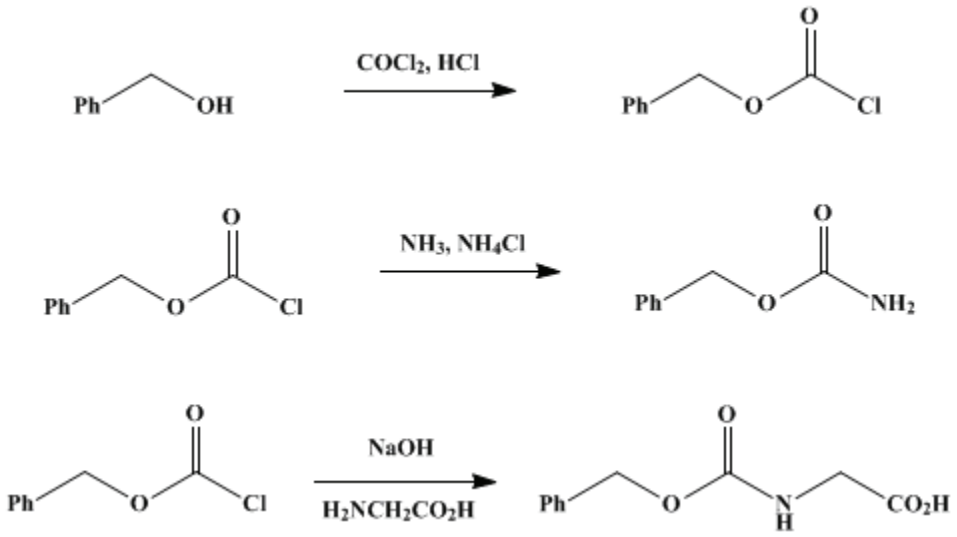
CARBOBENZOXY CHLORIDE AND DERIVATIVES

[Formic acid, chloro-, benzyl ester]



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1. Procedure

Caution! This procedure should be carried out in a hood.

A. *Benzyl chloroformate*. A 3-l. round-bottomed flask is fitted with a rubber stopper carrying an exit tube and a delivery tube extending to the bottom of the flask. The tubes are equipped with stopcocks so that the reaction flask may be disconnected. In the flask is placed 500 g. of dry toluene (Note 1), and the apparatus is weighed. The flask is then cooled in an ice bath, and phosgene (Note 2) is bubbled into the toluene until 109 g. (1.1 moles) has been absorbed (Note 3). The exit gases are passed through a flask containing toluene to remove any phosgene and then through a calcium chloride tube to a gas trap.

After the absorption of phosgene is completed the connection to the phosgene tank is replaced by a separatory funnel. The reaction flask is gently shaken while 108 g. (104 ml., 1 mole) of redistilled benzyl alcohol is added rapidly through the separatory funnel. The flask is allowed to stand in the ice bath for 30 minutes and at room temperature for 2 hours. The solution is then concentrated under reduced pressure, at a temperature not exceeding 60°, in order to remove hydrogen chloride, excess phosgene (Note 4), and the major portion of the toluene. The residue weighs 200–220 g. and contains 155–160 g. of benzyl chloroformate (91–94% based on the benzyl alcohol) (Note 5). The amount of benzyl chloroformate present in this solution may be estimated by preparing the amide from a small aliquot portion, or it may be safely calculated by assuming a minimum yield of 90% based on the benzyl alcohol used.

B. *Benzyl carbamate*. A measured aliquot (suitably 10 ml.) of the solution of benzyl chloroformate, prepared as described above, is added slowly and with vigorous stirring to 5 volumes of cold concentrated ammonium hydroxide (sp. gr. 0.90), and the reaction mixture is allowed to stand at room temperature for 30 minutes. The precipitate is filtered with suction, washed with cold water, and dried in a vacuum desiccator. The yield of practically pure benzyl carbamate, melting at 85–86°, is 7.0–7.2 g. (91–94% based on the benzyl alcohol used in A). Pure benzyl carbamate melting at 87° is obtained by recrystallizing the slightly impure material from 2 volumes of toluene.

C. *Carbobenzoxyglycine*. A solution of 7.5 g. (0.1 mole) of glycine in 50 ml. of 2 *N* sodium hydroxide is placed in a 200-ml. three-necked flask fitted with a mechanical stirrer and two dropping funnels. The flask is cooled in an, ice bath, and 17 g. (0.1 mole) of benzyl chloroformate (21–24 g. of the solution obtained in A) and 25 ml. of 4 *N* sodium hydroxide are added simultaneously to the vigorously stirred solution over a period of 20–25 minutes. The mixture is stirred for an additional 10 minutes. The toluene layer is separated, and the aqueous layer is extracted once with ether. The aqueous solution is cooled in an ice bath and acidified to Congo red with concentrated hydrochloric acid (Note 6). The precipitate is filtered, washed with small portions of cold water, and dried in the air. It is practically pure carbobenzoxyglycine; it weighs 18–19 g. (86–91%) and melts at 119–120°. The material may be recrystallized from chloroform; it then melts at 120° (Note 7).

2. Notes

1. The toluene may be dried by distillation.
2. Commercial phosgene was used; it was obtained in a tank from the Ohio Chemical Company.
3. The phosgene is absorbed rapidly for some time, then more slowly as the concentration increases. About 1 hour is required for this step. The amount of phosgene absorbed is checked by weighing the flask and delivery tubes occasionally.
4. In order to prevent the escape of phosgene, a toluene trap is inserted between the apparatus and the water pump. For this purpose it is convenient to use a 2-l. flask immersed in an ice bath and containing about 1 l. of toluene. The flask is fitted with an inlet tube reaching almost to the bottom.
5. It is not practical to remove the toluene completely; moreover, toluene does not interfere in the preparation of the derivatives.
6. The derivative may precipitate as an oil. However, crystallization is readily induced by cooling and scratching.
7. Carbobenzoxyalanine (m.p. 114–115°) is obtained in 80–90% yield from alanine and benzyl chloroformate by the same procedure.

3. Discussion

Benzyl chloroformate has been prepared by action of phosgene on benzyl alcohol.[1,2,3] The methods described here for the preparation of benzyl chloroformate and the carbobenzoxy derivatives of glycine and alanine are essentially those of Bergmann and Zervas.[2] The carbobenzoxy derivatives of other amino acids are conveniently prepared in the same way. Benzyl carbamate has been prepared by the action of ammonia on benzyl chloroformate.[1,4] The present method is that of Martell and Herbst.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 788

References and Notes

1. Thiele and Dent, *Ann.*, **302**, 257 (1898).
2. Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).
3. Farthing, *J. Chem. Soc.*, **1950**, 3213.
4. Martell and Herbst, *J. Org. Chem.*, **6**, 882 (1941).

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

carbobenzoxy derivatives of glycine

hydrogen chloride,
hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

alanine (56-41-7)

toluene (108-88-3)

phosgene (75-44-5)

Benzyl alcohol (100-51-6)

ammonium hydroxide (1336-21-6)

Glycine (513-29-1)

Carbobenzoxy chloride,
Formic acid, chloro-, benzyl ester,
benzyl chloroformate (501-53-1)

Benzyl carbamate (621-84-1)

carbobenzoxyglycine (1138-80-3)

Carbobenzoxyalanine