



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.

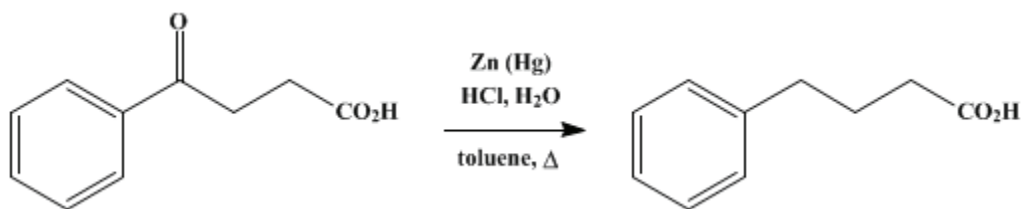
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 2, p.499 (1943); Vol. 15, p.64 (1935).

γ -PHENYLBUTYRIC ACID

[Butyric acid, γ -phenyl-]



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1. Procedure

Amalgamated zinc is prepared by shaking for five minutes a mixture of 120 g. of mossy zinc, 12 g. of mercuric chloride, 200 cc. of water, and 5–6 cc. of concentrated hydrochloric acid contained in a 1-l. round-bottomed flask. The solution is decanted and the following reagents are added, in the order named, to the zinc: 75 cc. of water, 175 cc. of concentrated hydrochloric acid, 100 cc. of toluene, and 50 g. (0.28 mole) of β -benzoylpropionic acid (p. 81). The flask is fitted with a vertical condenser connected to a gas absorption trap (Note 1), and the reaction mixture is boiled vigorously for twenty-five to thirty hours (Note 2). Three 50-cc. portions of concentrated hydrochloric acid are added at approximately six-hour intervals during the refluxing period.

After cooling to room temperature the layers are separated. The aqueous layer is diluted with 200 cc. of water and extracted with three 75-cc. portions of ether. The toluene layer and the ether extracts are combined, washed with water, and dried over calcium chloride. The solvents are removed by distillation under reduced pressure on the steam bath, after which the γ -phenylbutyric acid is distilled at 178–181°/19 mm. (148–154°/8–10 mm., 125–130°/3 mm.). The yield of acid, which melts at 46–48° (Note 3), is 38–41 g. (82–89 per cent of the theoretical amount) (Note 4).

2. Notes

1. Considerable hydrogen chloride is driven off during the initial heating, and it might appear that it would be advantageous to use constant-boiling instead of concentrated hydrochloric acid. If this is done, however, the product has a melting point of 40–44° and the yield is somewhat lower.
2. If the refluxing is interrupted for any reason, great care must be exercised to avoid frothing on heating again. The upper part of the flask may be occasionally brushed with a free flame. Once the two layers are well mixed, boiling proceeds smoothly.
3. The recorded melting points vary from 47° to 51°. The acid may be crystallized from hot water (75 cc. per g.) but the recovery is only about 50 per cent. No other suitable solvent or combination of solvents was discovered. Redistillation raises the melting point to 47–48° with only mechanical losses.
4. The procedure described differs from that published in *Org. Syn.* 15, 64, by the addition of toluene to the reaction mixture. In the presence of toluene the concentration of organic material in the aqueous layer is extremely small and polymolecular reactions take place to a smaller extent than in the original procedure. As a result the yield of pure product is greater.

When the modified procedure is applied to the preparation of higher-melting compounds, for example the γ -naphthylbutyric acids, the layers are separated after cooling to 50–60°, benzene is used for the extraction, and the combined benzene-toluene solution is clarified with Norite while still wet; it is then concentrated somewhat and allowed to cool for crystallization. In preparing methoxylated acids, such as γ -anisyl- or γ -veratrylbutyric acid, some demethylation occurs. When this happens the toluene layer and extracts are mixed with an excess of dilute sodium hydroxide solution and the organic solvents are removed by steam distillation. The alkaline solution is treated at 80° with an excess of methyl sulfate,

the solution is clarified with [Norite](#), cooled, and acidified, whereupon the product separates in good condition.

3. Discussion

Of the several methods by which [\$\gamma\$ -phenylbutyric acid](#) has been obtained, those of preparative value are the decarboxylation of [\$\gamma\$ -phenylethylmalonic acid](#);¹ the carbonation of [\$\gamma\$ -phenylpropylmagnesium bromide](#);² and the reduction of [\$\beta\$ -benzoylpropionic acid](#) with amalgamated zinc and [hydrochloric acid](#)³ or of its hydrazone with [sodium ethoxide](#).⁴ The use of [toluene](#) in the Clemmensen reduction of [\$\beta\$ -benzoylpropionic acid](#) and almost a score of related compounds has been described by Martin.⁵

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 2, 194](#)
- [Org. Syn. Coll. Vol. 2, 569](#)
- [Org. Syn. Coll. Vol. 3, 300](#)
- [Org. Syn. Coll. Vol. 4, 898](#)

References and Notes

1. Fischer and Schmitz, *Ber.* **39**, 2212 (1906).
2. Grignard, *Compt. rend.* **138**, 1049 (1904); Rupe and Proske, *Ber.* **43**, 1233 (1910).
3. Krollpfeiffer and Schäfer, *ibid.* **56**, 620 (1923).
4. Staudinger and Müller, *ibid.* **56**, 713 (1923).
5. Martin, *J. Am. Chem. Soc.* **58**, 1438 (1936).

Appendix

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

amalgamated zinc

benzene-toluene

γ -naphthylbutyric acids

γ -anisyl- or γ -veratrylbutyric acid

γ -phenylethylmalonic acid

[calcium chloride \(10043-52-4\)](#)

[hydrogen chloride,](#)
[hydrochloric acid \(7647-01-0\)](#)

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

[ether \(60-29-7\)](#)

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

Norite (7782-42-5)

toluene (108-88-3)

zinc (7440-66-6)

sodium ethoxide (141-52-6)

mercuric chloride (7487-94-7)

methyl sulfate (75-93-4)

β -Benzoylpropionic acid (2051-95-8)

γ -Phenylbutyric acid,
Butyric acid, γ -phenyl- (1821-12-1)

γ -phenylpropylmagnesium bromide