



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.

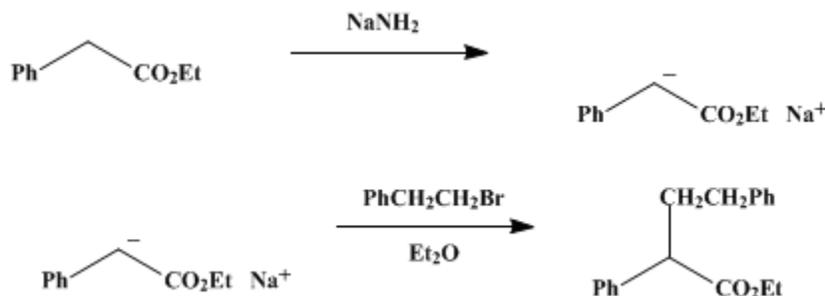
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 5, p.559 (1973); Vol. 47, p.72 (1967).

ETHYL 2,4-DIPHENYLBUTANOATE

[Butyric acid, 2,4-diphenyl-, ethyl ester]



Submitted by Edwin M. Kaiser, William G. Kenyon, and Charles R. Hauser¹.
Checked by Joseph G. Pfeiffer and Kenneth B. Wiberg.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A suspension of sodium amide² (0.1 mole) in liquid ammonia is prepared in a 500-ml. three-necked, round-bottomed flask fitted with a West condenser, a ball and socket glass mechanical stirrer (Note 1), and a dropping funnel. In the preparation of this reagent a small piece of clean sodium metal is added to 350 ml. of commercial anhydrous liquid ammonia. After the appearance of a blue color, a few crystals of hydrated ferric nitrate are added, whereupon the blue color is discharged. The remainder of the 2.3 g. (0.1 mole) of sodium (Note 2) is then rapidly added as small pieces. After all the sodium has been converted to sodium amide (Note 3), a solution of 16.4 g. (0.1 mole) of ethyl phenylacetate (Note 4) in 35 ml. of anhydrous ethyl ether is added dropwise over a 2-minute period, and the mixture is stirred for 20 minutes. To the dark green suspension is added over an 8-minute period a solution of 18.5 g. (0.1 mole) of (2-bromoethyl) benzene (Note 4) dissolved in 35 ml. of anhydrous ethyl ether. The mixture is stirred for 3 hours and is then neutralized by the addition of 5.35 g. (0.1 mole) of ammonium chloride. After addition of 150 ml. of dry ethyl ether, the ammonia is evaporated with stirring by use of a warm water bath (Note 5). The mixture is then cooled to 0° by an ice bath and hydrolyzed by the dropwise addition of 100 ml. of 3*N* hydrochloric acid. After stirring for 15 minutes, the mixture is allowed to warm to room temperature, and the layers are separated. The aqueous layer is extracted with two 50-ml. portions of ethyl ether. The combined ether extracts are then washed with two 50-ml. portions of saturated aqueous sodium bicarbonate followed by two 50-ml. portions of saturated sodium chloride. Drying is accomplished over magnesium sulfate. After filtration and solvent removal, the crude product is purified by vacuum distillation to give 20.6–21.8 g. (77–81%) of ethyl 2,4-diphenylbutanoate, b.p. 168–169° (3.5 mm.). Vapor phase chromatography shows the presence of one peak (Note 6).

2. Notes

1. Stirrers with Teflon paddles should not be used.
2. The sodium was weighed in toluene and then rinsed in anhydrous ethyl ether.
3. Conversion is indicated by the discharge of the blue color.
4. Ethyl phenylacetate and (2-bromoethyl)benzene as supplied by Eastman Organic Chemicals were used without further purification.
5. Alternatively, the ammonia may be evaporated after the ammonium chloride and ethyl ether have been added by allowing the flask to stand overnight with stirring.
6. A 5-ft. Apiezon L column at 225° was used.

3. Discussion

The procedure described is a modification of that given by Kenyon, Meyer, and Hauser.³ No other methods appear to have been used to prepare ethyl 2,4-diphenylbutanoate. A number of alkylations of ethyl phenylacetate have previously been effected with alkyl halides by means of other basic reagents, but the yields generally have not been very satisfactory.^{4,5}

4. Merits of the Preparation

The method described is successfully used for the alkylation and aralkylation of ethyl and *t*-butyl phenylacetate.³ The alkylation of ethyl phenylacetate with methyl iodide, *n*-butyl bromide, benzyl chloride, and α -phenylethyl chloride affords the corresponding pure monoalkylation products in 69%, 91%, 85%, and 70% (*erythro* isomer) yields, respectively. The alkylation of *t*-butyl phenylacetate with methyl iodide, *n*-butyl bromide, α -phenylethyl chloride, and β -phenylethyl bromide gives the corresponding pure monoalkylated products in 83%, 86%, 72–73%, and 76% yields, respectively.

Certain of the monoalkylated ethyl phenylacetates have been further alkylated with alkyl and aralkyl halides to produce the corresponding disubstituted phenylacetic esters.⁶ Ethyl 2-phenylpropanoate has been alkylated by methyl iodide to give pure ethyl 2-methyl-2-phenylpropanoate in 81% yield. Similarly, the alkylations of ethyl 2-phenylhexanoate with methyl iodide, *n*-butyl bromide, and benzyl chloride gave the corresponding pure dialkylated products in 73%, 92%, and 72% yields, respectively.

Butylation of ethyl phenylacetate, *t*-butyl phenylacetate, and ethyl 2-phenylhexanoate has also been accomplished with *n*-butyl bromide and sodium hydride in refluxing monoglyme in 64%, 66%, and 56% yields, respectively.⁶ In contrast to the sodium amide reactions above, however, careful fractionation of the crude products was required to obtain pure products.

This preparation is referenced from:

- *Org. Syn. Coll. Vol. 5, 526*

References and Notes

1. Department of Chemistry, Duke University, Durham, North Carolina. This work was supported by the U. S. Army Research Office — Durham.
2. C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).
3. W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).
4. A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, **9**, 284 (1957).
5. A. L. Mndzhoyan, O. L. Mndzhoyan, E. R. Bagdasaryan, and V. A. Mnatsakanyan, *Dokl. Akad. Nauk Arm. SSR*, **30**, 97 (1960) [*C.A.* **55**, 3508 (1961)].
6. W. G. Kenyon, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, **30**, 2937 (1965).

Appendix

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

ethyl and *t*-butyl phenylacetate

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether,
ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

n-butyl bromide (109-65-9)

toluene (108-88-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

Methyl iodide (74-88-4)

Ethyl phenylacetate (101-97-3)

magnesium sulfate (7487-88-9)

β -phenylethyl bromide,
(2-bromoethyl)benzene,
(2-bromoethyl) benzene (103-63-9)

sodium amide (7782-92-5)

ferric nitrate

sodium hydride (7646-69-7)

α -phenylethyl chloride (672-65-1)

Ethyl 2,4-diphenylbutanoate,
Butyric acid, 2,4-diphenyl-, ethyl ester (53608-81-4)

Ethyl 2-phenylpropanoate

ethyl 2-methyl-2-phenylpropanoate

ethyl 2-phenylhexanoate

t-butyl phenylacetate