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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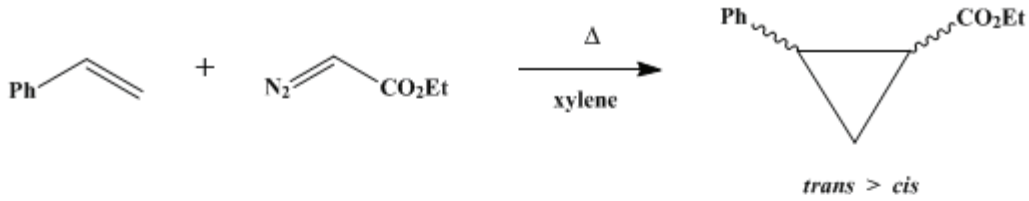
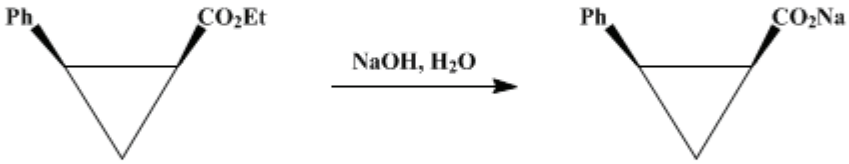
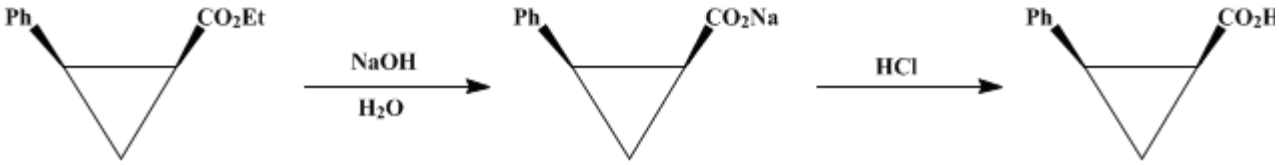
cis-2-PHENYLCYCLOPROPANECARBOXYLIC ACID

[Cyclopropanecarboxylic acid, 2-phenyl-, *cis*-]







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1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Ethyl* cis- *and* trans-2-*phenylcyclopropanecarboxylate*. Xylene (500 ml., (Note 1)) is heated to reflux in a 2-l. flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser. A solution of 179 g. (1.57 moles) of ethyl diazoacetate [*Org. Synth.*, **Coll. Vol. 4**, 424 (1963)] (Note 2) and 163 g. (1.57 moles) of styrene (Note 3) is placed in the dropping funnel and added dropwise to the refluxing, stirred xylene over a period of 90 minutes. After addition is complete, the solution is stirred and heated at the reflux temperature for an additional 90 minutes (Note 4). Xylene is removed under reduced pressure, and the residual red oil is distilled through a short Vigreux column. The fraction boiling at 85–93° (0.5 mm.) is collected, yielding 155 g. (52%) of colorless product, n_D^{26} 1.5150, n_D^{20} 1.5166 (Note 5) and (Note 6).

B. cis-2-*Phenylcyclopropanecarboxylic acid*. A 1-l., three-necked flask equipped with a dropping funnel, stirrer, and a short Vigreux column (Note 7), to which is attached a partial take-off distilling head with reflux condenser, is charged with 155 g. (0.816 mole) of ethyl *cis*- and *trans*-2-phenylcyclopropanecarboxylate, 200 ml. of ethanol, 65 ml. of water, and 24.5 g. (0.612 mole) of sodium hydroxide pellets (Note 8). The mixture is heated at the reflux temperature for 5 hours during which time 200 ml. of ethanol is slowly distilled and replaced by an equal volume of water added through the dropping funnel. Heating is discontinued, 250 ml. of water and 150 ml. of benzene are added, and the

mixture is stirred for 2–3 minutes. The layers are separated, and the aqueous layer is washed with two 50-ml. portions of benzene (Note 9).

The benzene extracts are placed in the apparatus used above, and 130 ml. of water and 13 g. (0.32 mole) of sodium hydroxide pellets are added. Benzene (200 ml.) is distilled and then the 200 ml. of ethanol obtained in the initial hydrolysis is added. The reflux-distillation process is continued for 5 hours, during which time 250 ml. of distillate is obtained. The mixture is cooled, and 65 ml. of benzene and 30 ml. of concentrated hydrochloric acid are added. The layers are separated, and the aqueous solution is washed twice with 35-ml. portions of benzene. The combined benzene extracts are concentrated and dried by distillation of 90 ml. of benzene. The hot concentrate is decanted from a trace of salt, 70 ml. of petroleum ether is added, and the resulting solution is stored overnight at 0°. Filtration of the solid from the cold petroleum ether solution and washing with a small volume of cold 50:50 benzene–petroleum ether yields 19.5–23.8 g. (14.6-20.7% based on the mixed ester used, or 38–46.4% based on the *cis* ester, (Note 10)) of *cis*-2-phenylcyclopropanecarboxylic acid, m.p. 106–109° (Note 11). An additional 2–3 g. of the *cis* acid may be obtained by concentrating the mother liquors to low volume, adding petroleum ether, and chilling the resulting solution for several days.

2. Notes

1. The checkers used xylene distilled from sodium.
2. Ethyl diazoacetate is available from Aldrich Chemical Co. *Diazoacetic esters are potentially explosive and, therefore, must be handled with caution.* [See *Org. Synth.*, **Coll. Vol. 4**, 424 (1963).]
3. Redistilled styrene, b.p. 52–3° (28 mm.) was used by the submitters. The checkers used reagent grade styrene obtained from Eastman Organic Chemicals without further purification.
4. Refluxing was discontinued after nitrogen evolution ceased.
5. GC of several samples of the mixed ester revealed a composition of 55–65% *trans*-, 30–40% *cis*-ester, and 5% impurities.
6. The checker obtained 204 g. of product (68% yield), n_D^{26} 1.5160, with the approximate composition 39% *cis*–60% *trans*-ester.
7. The checkers used a 50-cm. Vigreux column.
8. The amount of base used is 0.75 mole per mole of mixed esters. This is slightly more than necessary to saponify all the *trans*-ester, present. Since the *trans*-ester is saponified more rapidly than the *cis*-ester, this affords an effective separation of the isomer. This procedure is a modification of that of Walborsky and Plonsker.[2]
9. *trans*-2-Phenylcyclopropanecarboxylic acid may be obtained from the aqueous solution in the following way. The aqueous solution is treated with 65 ml. of concentrated hydrochloric acid, and the mixture is extracted with one 130-ml. portion of benzene and two 20-ml. portions of benzene. The carefully separated benzene layers are combined and dried by distilling 100 ml. of benzene. The resulting solution is decanted from the small amount of salt present and diluted with 200 ml. of petroleum ether. The resulting solution is cooled at 0° overnight, and the precipitate is collected and washed with a small amount of a cold, 50:50 mixture of petroleum ether–benzene, yielding 63–65 g. (80% based on *trans*-ester originally present) of needles, m.p. 87–93°. Recrystallization of this product several times from carbon tetrachloride–petroleum ether gives the pure *trans*-acid, m.p. 93°.
10. The submitters obtained 25–28 g. of *cis*-acid (19–21% based on the mixed ester used).
11. Burger and Yost[3] reported m.p. 106–107° for pure *cis*-2-phenylcyclopropanecarboxylic acid and m.p. 93° for pure *trans*-2-phenylcyclopropanecarboxylic acid.

3. Discussion

The method described is a modification of that described by Walborsky and Plonsker.[2] It is based on the more rapid hydrolysis, due to less steric hindrance, of the *trans*- over the *cis*-ester. The *cis*-acid has also been obtained by fractional crystallization of the mixed acids.[3]

The present method offers a convenient preparation of *cis*-2-phenylcyclopropanecarboxylic acid that is amenable to large-scale work. The process above has been carried out by the submitters on a twentyfold scale with essentially the same results. The method also provides an example of the separation of two isomers based on differences in reaction rate.

References and Notes

1. Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101.
2. H. M. Walborsky and L. Plonsker, *J. Am. Chem. Soc.*, **83**, 2138 (1961).
3. A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).

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

petroleum ether

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

sodium (13966-32-0)

xylene (106-42-3)

styrene (100-42-5)

ethyl diazoacetate (623-73-4)

cis-2-Phenylcyclopropanecarboxylic acid,
Cyclopropanecarboxylic acid, 2-phenyl-, cis- (939-89-9)

trans-2-Phenylcyclopropanecarboxylic acid (939-90-2)

Ethyl cis- and trans-2-phenylcyclopropanecarboxylate (946-39-4)