



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](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.

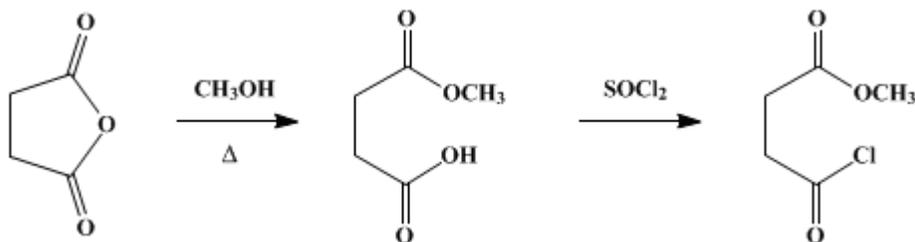
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 3, p.169 (1955); Vol. 25, p.19 (1945).*

## β-CARBOMETHOXYPROPIONYL CHLORIDE

[Propionic acid, β-(chloroformyl)-, methyl ester]



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Checked by C. F. H. Allen and C. V. Wilson.

### 1. Procedure

A. *Methyl hydrogen succinate*. A mixture of 400 g. (4 moles) of succinic anhydride (Note 1) and 194 ml. (4.8 moles) of methanol (Note 2) in a 1-l. round-bottomed flask is refluxed on a steam bath. After about 35 minutes the mixture is swirled frequently until it becomes homogeneous (this requires 15–30 minutes); the flask is then half immersed in the steam bath for an additional 30–25 minutes (Note 3).

The excess methanol is removed by distillation under reduced pressure (water pump) from a steam bath, and the residual liquid is poured into an 18- to 25-cm. evaporating dish which is cooled in a shallow pan of cold water. As the half ester crystallizes, it is stirred and scraped off the dish in order to prevent formation of a solid cake. After being dried to constant weight in a vacuum desiccator (5–8 days), the product weighs 502–507 g. (95–96%) and melts at 57–58° (Note 4) and (Note 5).

B. *β-Carbomethoxypropionyl chloride*. In a 1-l. flask (Note 6) bearing a reflux condenser are placed 264 g. (2 moles) of methyl hydrogen succinate and 290 ml. (4 moles) of thionyl chloride (Note 7), and the solution is warmed in a bath at 30–40° for 3 hours (Note 8). The condenser is replaced by a modified Claisen still head, the excess thionyl chloride is removed on a steam bath under reduced pressure, and the β-carbomethoxypropionyl chloride is distilled (Note 9) and (Note 10). The yield of colorless product is 270–278 g. (90–93%), b.p. 92–93°/18 mm. (Note 11) and (Note 12).

### 2. Notes

1. Eastman's succinic anhydride (m.p. 115–116°) was used.
2. Synthetic methanol was used. Since this anhydrous alcohol is hygroscopic, partly filled bottles that have been opened intermittently in the laboratory should be rejected.
3. Thirty minutes is allowed if solution resulted after 15 minutes of swirling; 25 minutes if 30 minutes was needed for homogeneity.

The time factor is very important. In one run in which the mixture was heated for a total of 55 minutes, a product was obtained which was shown by titration to contain about 6% of anhydride. Longer heating than that specified increases the yield of diester. Any change in quantity of materials used may necessitate a new set of conditions in order to obtain the maximum yield.

4. The checkers prefer the following procedure, which can be carried through in one day. A suspension of approximately one-half of the crude product in 750 ml. of carbon disulfide is warmed on a steam bath; two layers form, in which some solid remains in suspension. This is dissolved by the addition of 350 ml. of ether. The whole is chilled to 0°, and the solid is filtered by suction. The other half of the crude product is now dissolved in this filtrate, the solution is again chilled to 0°, and the solid is filtered. The combined yield of acid ester, m.p. 57–58°, is 438–449 g. (83–85%). A further 32–37 g. (6–7%) of less pure material (m.p. 56–57°) can be obtained by concentrating the filtrate to half its volume and chilling to 0°.

5. The product, which is sufficiently pure for the next step, contains at least 98% methyl hydrogen succinate as shown by titration or distillation through an 18-in. Podbielniak-type column.
6. Equipment with ground-glass joints is used throughout.
7. Eastman's thionyl chloride (b.p. 75–76°) was used. The checkers obtained equivalent yields of the chloride by using only 20% excess of thionyl chloride. The mixture was heated for 1 hour at 40°, allowed to stand overnight, and heated again for 2 hours at 40°.
8. Since hydrogen chloride is evolved, it is advisable to work in a hood or employ a gas trap.
9. An electric heating mantle is convenient.
10. Other boiling points are 85.5–87°/13 mm. and 89–90°/15 mm. The use of as low a pressure as possible is advisable, since the substance tends to lose methyl chloride and form succinic anhydride.
11. The submitter obtained the same yield when phosphorus pentachloride was used instead of thionyl chloride. Consistent results were obtained with the former reagent only when the acid chloride was distilled at pressures below 3 mm. (b.p. 58–59°/2.5 mm.).
12. Methyl hydrogen glutarate, ethyl hydrogen adipate, and ethyl hydrogen sebacate may be converted to the corresponding ester acid chlorides by this procedure in about the same yields. Distillation should be carried out rapidly at a pressure of 4 mm. or lower.

### 3. Discussion

Methyl hydrogen succinate has been prepared by heating succinic acid with methyl succinate,<sup>1</sup> by treating ethyl succinate with sodium methoxide,<sup>2</sup> and by heating succinic anhydride with methanol.<sup>3,4,5,6</sup>

$\beta$ -Carbomethoxypropionyl chloride has been prepared from methyl hydrogen succinate by the use of thionyl chloride<sup>4,6</sup> or phosphorus pentachloride.<sup>5</sup>

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 601
- Org. Syn. Coll. Vol. 3, 613

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### References and Notes

1. Fourneau and Sabetay, *Bull. soc. chim. France*, (4) **45**, 841 (1929).
  2. Komnenos, *Monatsh.*, **32**, 77 (1911).
  3. Bone, Sudborough, and Sprankling, *J. Chem. Soc.*, **85**, 539 (1904).
  4. Nenitzescu, Cioranescu, and Przemetsky, *Ber.*, **73B**, 313 (1940).
  5. Cason, *J. Am. Chem. Soc.*, **64**, 1106 (1942).
  6. Ruggli and Maeder, *Helv. Chim. Acta*, **25**, 936 (1942).
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### Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

ethyl succinate

Ethyl hydrogen adipate (626-86-8)

methyl chloride (74-87-3)

Succinic acid (110-15-6)

sodium methoxide (124-41-4)

carbon disulfide (75-15-0)

Succinic anhydride (108-30-5)

Ethyl hydrogen sebacate (693-55-0)

$\beta$ -Carbomethoxypropionyl chloride,  
Propionic acid,  $\beta$ -(chloroformyl)-, methyl ester (1490-25-1)

Methyl hydrogen succinate,  
methyl succinate (3878-55-5)

Methyl hydrogen glutarate (1501-27-5)