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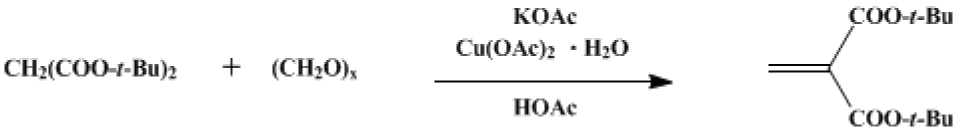
*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

DOI:10.15227/orgsyn.064.0063

*Organic Syntheses, Coll. Vol. 7, p.142 (1990); Vol. 64, p.63 (1986).*

# DI-*tert*-BUTYL METHYLENEMALONATE

## [Propanedioic acid, methylene-, bis(1,1-dimethylethyl)ester]



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Checked by Doreen L. Weller and James D. White.

## 1. Procedure

*Caution! This reaction should be carried out in an efficient hood to prevent exposure to formaldehyde and acetic acid.*

A 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirrer and a reflux condenser protected by a calcium chloride drying tube. Into the flask are placed 30.0 g (0.14 mol) of di-*tert*-butyl malonate (Note 1), 8.4 g (0.28 mol) paraformaldehyde (Note 2), 1.4 g (0.014 mol) of potassium acetate, 1.4 g (0.007 mol) of cupric acetate monohydrate, and 70 mL of glacial acetic acid. The resulting green–white suspension is placed in an oil bath preheated to 90–100°C and stirred for 2 hr (Note 3). The reaction mixture is allowed to cool to room temperature, and the reflux condenser is replaced with a short-path distillation apparatus, the vacuum outlet of which is connected in sequence to a trap cooled in acetone–dry ice, a potassium hydroxide trap, another trap cooled in acetone–dry ice, and a vacuum pump. The receiving flask is cooled in acetone–dry ice, and the system is evacuated over approximately 1 hr to remove acetic acid and other volatile material (Note 4). The bath temperature is increased to 40–50°C for 15 min and then is rapidly raised to 140–150°C to drive over crude product, which is collected over a boiling-point range of 60–82°C (Note 5). When distillate ceases to come over, the bath temperature is increased to 170°C and distillate is collected over the same boiling-point range until the reaction mixture turns from blue to green–brown. The total amount of crude product collected is 24.3 g. This material is dissolved in 50 mL of ether and washed with saturated aqueous sodium bicarbonate solution (4 × 20 mL) and water (25 mL). The combined aqueous fractions are extracted with 50 mL of ether, and the combined ether extracts are dried over magnesium sulfate for 10 min (Note 6). Filtration and evaporation on a rotary evaporator give 20.0 g of crude product, which is distilled through an 8-cm Vigreux column. The di-*tert*-butyl methylenemalonate is collected at 60–67°C/0.1 mm and weighs 15.3 g (48%) (Note 7). The product is somewhat unstable and should be stored in Pyrex in the refrigerator.

## 2. Notes

1. Di-*tert*-butyl malonate was prepared according to the procedure of Johnson; see *Org. Synth., Coll. Vol. IV* **1963**, 261.
2. Paraformaldehyde was obtained from Aldrich Chemical Company, Inc., and stored in a desiccator over phosphorus pentoxide.
3. After approximately 25 min, the suspension dissolves and the reaction mixture becomes blue–green.
4. At the beginning of the evaporation, the pressure is controlled to minimize bumping of the vigorously boiling mixture.
5. During this operation the pressure varies between 0.3 and 1.5 mm. As the temperature is raised, the reaction mixture turns blue and gas evolution is observed.
6. The procedure can be interrupted at this point and the ether extracts dried over magnesium sulfate overnight in the refrigerator.
7. The bath temperature should not exceed 100°C in order to prevent contamination of the product with the bis(hydroxymethyl) derivative of di-*tert*-butyl malonate. The product exhibits single peaks in the $^1$H NMR spectrum ($CDCl_3$, 250 MHz) at 1.51 and 6.25 ppm and contains approximately 6% of di-*tert*-butyl

malonate as indicated by a peak at 1.47 ppm. Contamination by the bis(hydroxymethyl) derivative is indicated by a peak at 1.48 ppm.

## 3. Discussion

Methylenemalonate esters are potentially useful activated alkenes that can serve as electrophilic partners in the Michael and cycloaddition reactions and, in the process, introduce a *gem*-diester functionality for further synthetic transformation. The simple esters, however, have a marked propensity toward spontaneous polymerization and, as a consequence, have been used only sparingly in the Michael reaction,[2 3 4 5] the Diels–Alder reaction,[6 7 8] [2 + 2] cycloaddition,[9] and [3 + 2] cycloaddition.[10 11 12 13 14 15] The recently prepared di-*tert*-butyl analog[16] is advantageous in being longer lived and suitable for conventional synthetic operations, and in introducing a readily cleaved diester moiety. In its most useful application thus far, the compound has been found to react under mild conditions with enamines with no added catalyst or with enol ethers and acetates under Lewis acid catalysis to give either cyclobutanes or Michael adducts, depending on alkene structure.[17]

Di-*tert*-butyl methylenemalonate was originally prepared by phenylsulfenylation of di-*tert*-butyl methylmalonate and thermal elimination of the related sulfoxide.[16] Because methylenemalonate esters are customarily prepared by Knoevenagel-type condensation of malonic esters with formaldehyde equivalents, the considerably more convenient procedure described herein was subsequently adapted from Bachman and Tanner's study using paraformaldehyde under metal-ion catalysis.[6] The approximately 6% di-*tert*-butyl malonate accompanying the product has presented no interference in the aforementioned reactions with nucleophilic alkenes under neutral or acidic conditions, but its presence should be taken into consideration in other applications.

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## References and Notes

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

## (Registry Number)

cyclobutanes

methylenemalonate esters

acetic acid (64-19-7)

ether (60-29-7)

formaldehyde (50-00-0)

sodium bicarbonate (144-55-8)

magnesium sulfate (7487-88-9)

potassium acetate (127-08-2)

cupric acetate monohydrate (6046-93-1)

Propanedioic acid, methylene-, bis(1,1-dimethylethyl)ester,
Di-tert-butyl methylenemalonate (86633-09-2)

phosphorus pentoxide (1314-56-3)

Di-tert-butyl malonate (541-16-2)

di-tert-butyl methylmalonate

paraformaldehyde (30525-89-4)