



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.

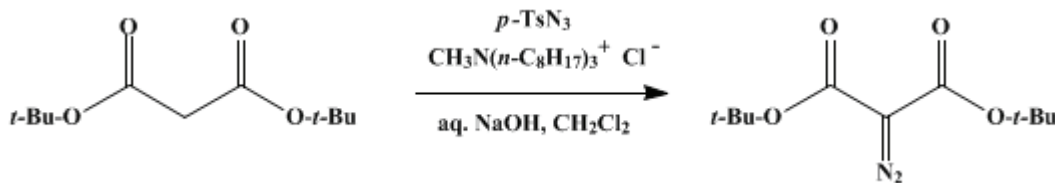
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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. 6, p.414 (1988); Vol. 59, p.66 (1979).

DIAZO TRANSFER BY MEANS OF PHASE-TRANSFER CATALYSIS: **DI-*tert*-BUTYL DIAZOMALONATE**

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



Submitted by Henry J. Ledon¹

Checked by Steven J. Hobbs and Robert M. Coates.

1. Procedure

Caution! Diazomalonic esters are toxic and potentially explosive. They must be handled with care. This preparation should be carried out in a well-ventilated hood, and the distillation of di-tert-butyl diazomalonate should be conducted behind a safety shield.

A 500-ml., three-necked, round-bottomed flask equipped with a reflux condenser, a dropping funnel, an argon inlet, and a Teflon-coated magnetic stirring bar is charged with 10.8 g. (0.0500 mole) of di-*tert*-butyl malonate (Note 1), 9.9 g. (0.0502 mole) of *p*-toluenesulfonyl azide (Note 2), 0.5 g. (0.001 mole) of methyltri-*n*-octylammonium chloride (Note 3), and 200 ml. of dichloromethane (Note 4). The solution is stirred vigorously as the flask is flushed with argon for 10 minutes, then 10 ml. (0.1 mole) of aqueous 10 *N* sodium hydroxide is added in one portion (Note 5). The mixture is stirred for 2 hours, during which time it changes from colorless to pale yellow. A 200-ml. portion of water is added; the organic layer is separated, washed with three 500-ml. portions of water (Note 6), and dried with anhydrous magnesium sulfate. After filtration of the drying agent, the solvent is removed on a rotary evaporator using a water bath kept at 30° (Note 7). The residual yellow-orange liquid is distilled at high vacuum (Note 8). The temperature of the heating bath is gradually raised to *ca.* 70° and kept at 70–75° during the distillation. After separation of a small forerun, 7.2–7.6 g. (59–63%) of di-*tert*-butyl diazomalonate is collected, b.p. 44–45° (0.02 mm.), $n_D^{22} = 1.4568$ (Note 9) and (Note 10).

2. Notes

1. Di-*tert*-butyl malonate is available commercially directly from Fluka AG, Buchs, Switzerland, or from its North American representative, Tridom Chemical Inc. Alternatively this compound may be prepared from malonic acid as described in *Org. Synth., Coll. Vol. 4*, 261 (1963).
2. *p*-Toluenesulfonyl azide was prepared according to the procedure in *Org. Synth., Coll. Vol. 5*, 179 (1973).
3. The submitter obtained methyltri-*n*-octylammonium chloride (Aliquat 336) from General Mills Company, Chemical Division, Kankakee, Illinois. The phase-transfer catalyst used by the checkers, which was supplied by Fluka AG through Tridom Chemical Inc., was a mixture in which the alkyl chains varied in length from *n*-octyl to *n*-decyl with the former predominating.
4. Reagent grade dichloromethane was used without further purification.
5. The sodium hydroxide solution was deoxygenated by bubbling a stream of argon through it for 10 minutes.
6. The organic layer is washed with relatively large portions of water to avoid difficulty in separating the phases. The checkers found that vigorous shaking during the extractions gave intractable emulsions. The emulsions were avoided by gentle swirling of the dichloromethane–water mixtures.
7. To avoid foaming during the distillation, the checkers removed the last traces of solvent by

evacuation at 0.1 mm. and room temperature for 12–24 hours.

8. The submitter recommends that the apparatus be purged with [argon](#) prior to the distillation.

9. The checkers collected foreruns amounting to 0.3–0.7 g., b.p. 50–58° (0.003 mm.) and 40–45° (0.0006 mm.). The product was collected in two or three fractions, b.p. 53–57° (0.002–0.011 mm.), 54–58° (0.002–0.003 mm.), and 45–52° (0.0004–0.0006 mm.). Inspection and integration of the ¹H NMR spectra of the foreruns indicated that the fractions were mainly [di-tert-butyl diazomalonate](#) contaminated with 16–35% of [di-tert-butyl malonate](#). The purest fractions usually crystallized on standing at room temperature to give a low-melting solid.

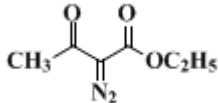
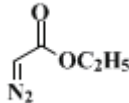
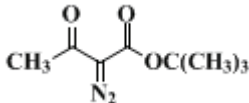
A GC analysis on the product by the submitter, using an 0.3 × 80 cm. column packed with 10% silicone rubber (SE-30) supported on acid-washed, 60–80 mesh Chromasorb P at 80°, exhibited a single peak. The retention times of [di-tert-butyl malonate](#), [di-tert-butyl diazomalonate](#), and [p-toluenesulfonyl azide](#) were 2, 6, and 9 minutes, respectively. The purity of the product obtained by the checkers was estimated from ¹H NMR spectra to be *ca.* 94%, the remainder being [di-tert-butyl malonate](#).

10. The spectral properties of the product are as follows: IR (liquid film) cm.⁻¹: 2137 (C=N₂), 1751 (C=O), 1730 (C=O), 1686; UV (C₂H₅OH) nm. max. (log ε): 255 (3.68); ¹H NMR (CDCl₃), δ (multiplicity, number of protons, assignment): 1.52 [s, 18H, 2C(CH₃)₃]; ¹³C NMR with proton decoupling (CDCl₃), δ (assignment): 28.5 (CH₃), 65.7 (C=N₂), 82.8 [C(CH₃)₃], 160.6 (C=O).

3. Discussion

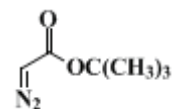
The "diazo transfer reaction" between [p-toluenesulfonyl azide](#) and active methylene compounds is a useful synthetic method for the preparation of α-diazo carbonyl compounds.² However, the reaction of [di-tert-butyl malonate](#) and [p-toluenesulfonyl azide](#) to form [di-tert-butyl diazomalonate](#) proceeded to the extent of only 47% after 4 weeks with the usual procedure.³ The present procedure, which utilizes a two-phase medium and [methyltri-*n*-octylammonium chloride](#) (Aliquat 336) as phase-transfer catalyst, effects this same diazo transfer in 2 hours and has the additional advantage of avoiding the use of anhydrous solvents.^{4,5} This procedure has been employed for the preparation of diazoacetoacetates, diazoacetates, and diazomalonates (Table I).⁵ Ethyl and *tert*-butyl acetoacetate are converted to the corresponding α-diazoacetoacetates with saturated [sodium carbonate](#) as the aqueous phase. When aqueous [sodium hydroxide](#) is used with the acetoacetates, the initially formed α-diazoacetoacetates undergo deacylation to the diazoacetates. Methyl esters are not suitable substrates, since they are too easily saponified under these conditions.

TABLE I
PREPARATION OF α-DIAZO CARBONYL COMPOUNDS VIA PHASE TRANSFER CATALYSIS^a

Starting Material	Organic Phase	Aqueous Phase	Phase Transfer Catalyst ^b	Time and Temperature	Product	Yield (%)
Ethyl acetoacetate	pentane	saturated Na ₂ CO ₃	A	15 hours, 25°		90
Ethyl acetoacetate	pentane	3 N NaOH	A	15 hours, 25°		53
tert-Butyl acetoacetate	pentane	saturated Na ₂ CO ₃	A	15 hours, 25°		77
	dichloromethane	3 N NaOH	B	1 hour, 0°		92
tert-Butyl	pentane	3 N	A	15 hours, 25°		89

acetoacetate

NaOH

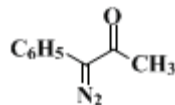
Phenyl
acetone

benzene

10 N
NaOH

A

15 hours, 0°



100

^aThese reactions were carried out with 0.005 mole of the carbonyl compound and 0.005 mole of *p*-toluenesulfonyl azide.

^bA, tetrabutylammonium bromide; B, methyltri-*n*-octylammonium chloride (Aliquat 336).

Although the hazardous properties of *di-tert-butyl diazomalonate* are not known with certainty, it is reasonable to assume that they are similar to those of diazoacetic esters, which are considered to be moderate explosion hazards when heated.⁶ Contact with rough or metallic surfaces should be avoided. The submitter has routinely distilled 10-g. quantities of *di-tert-butyl diazomalonate* under argon with no sign of decomposition.

Diazomalonate esters serve as intermediates for the synthesis of a wide variety of compounds including cyclopropanes,^{7 8 9,10 11} cyclopropenes,^{7,8,9,12} cycloheptatrienes,¹³ sulfur ylides,^{14 15} lactones,¹⁶ and substituted malonates.¹⁷

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 7, 438](#)
- [Org. Syn. Coll. Vol. 9, 400](#)

References and Notes

1. Laboratoire de Chimie de l'Ecole Normale Supérieure, 24, rue Lhomond, 75231 Paris Cedex 05, France. [Present address: Institut de Recherches sur la Catalyse, 79 Boulevard du 11 Novembre 1918, 69626 Villeurbanne Cedex, France.]
2. M. Regitz, J. Hocker, and A. Liedhegener, *Org. Synth.*, **Coll. Vol. 5**, 179 (1973).
3. B. W. Peace, F. Carman, and D. S. Wulfman, *Synthesis*, 658 (1971).
4. C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).
5. H. Ledon, *Synthesis*, 347 (1974).
6. N. I. Sax, "Dangerous Properties of Industrial Materials," 4th ed., Van Nostrand Reinhold, New York, 1975, p. 609.
7. For reviews see: (a) W. Kirmse, "Carbene Chemistry," 2nd ed., Academic Press, New York, 1971;
8. D. Wendisch, in E. Muller, Ed., "Methoden der Organischen Chemie" (Houben-Weyl), 4th ed., Vol. 4/3, Georg Thieme Verlag, Stuttgart, Germany, 1971;
9. V. Dave and E. Warnhoff, *Org. React.*, **18**, 217 (1970).
10. B. W. Peace and D. S. Wulfman, *Synthesis*, 137 (1973);
11. E. Wenkert, M. E. Alonso, B. L. Buckwalter, and K. J. Chou, *J. Am. Chem. Soc.*, **99**, 4778 (1977).
12. M. E. Hendrick, *J. Am. Chem. Soc.*, **93**, 6337 (1971); R. Breslow, R. Winter, and M. Battiste, *J. Org. Chem.*, **24**, 415 (1959).
13. M. Jones, Jr., W. Ando, M. E. Hendrick, A. Kulczycki, Jr., P. M. Howley, K. F. Hummel, and D. S. Malament, *J. Am. Chem. Soc.*, **94**, 7469 (1972).
14. For a review see W. Ando, *Acc. Chem. Res.*, **10**, 179 (1977);
15. J. Cuffe, R. J. Gillespie, and A. E. A. Porter, *J. Chem. Soc. Chem. Commun.*, 641 (1978).

16. W. Ando, I. Imai, and T. Migita, *J. Chem. Soc. Chem. Commun.*, 822 (1972).
17. H. Ledon, G. Linstumelle, and S. Julia, *Bull. Soc. Chim. Fr.*, 2065 (1973).
-

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

Ethyl and tert-butyl acetoacetate

Benzene (71-43-2)

sodium hydroxide,
NaOH (1310-73-2)

sodium carbonate,
Na₂CO₃ (497-19-8)

Ethyl acetoacetate (141-97-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

Malonic acid (141-82-2)

phenyl acetone (103-79-7)

magnesium sulfate (7487-88-9)

argon (7440-37-1)

n-Decyl

tetrabutylammonium bromide (1643-19-2)

Propanedioic acid, diazo-, bis(1,1-dimethylethyl) ester,
Di-tert-butyl diazomalonate (35207-75-1)

Methyltri-n-octylammonium chloride (5137-55-3)

p-toluenesulfonyl azide (941-55-9)

tert-Butyl acetoacetate (1694-31-1)

n-Octyl

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