



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.

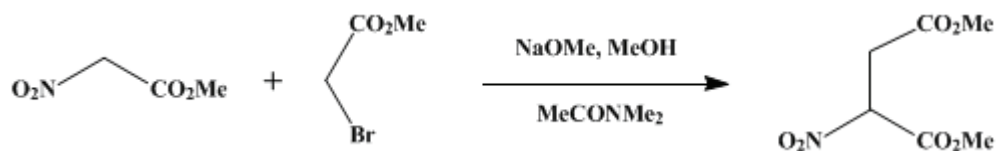
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.503 (1988); Vol. 57, p.60 (1977).

DIMETHYL NITROSUCCINATE

[Butanedioic acid, 2-nitro-, dimethyl ester]



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Checked by M. Braun and G. Büchi.

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 1-l., three-necked, round-bottomed flask equipped with a calcium chloride drying tube, a mechanical stirrer, and a ground-glass stopper is charged with 28.2 g. (0.184 mole) of freshly distilled methyl bromoacetate, 500 ml. of anhydrous *N,N*-dimethylacetamide (Note 1), and 20.0 g. (0.168 mole) of methyl nitroacetate (Note 2). The solution is stirred vigorously while 146 ml. (0.168 mole) of 1.15 *N* sodium methoxide in methanol is added in one portion. The resulting light-yellow suspension is stirred for an additional 16 hours at room temperature during which time it changes into a clear yellow solution.

After dilution with 200 ml. of benzene, the solution is transferred to a 2-l. separatory funnel containing 800 ml. of ice water and shaken thoroughly. The aqueous layer is separated, acidified to pH 3–4 with 2–3 ml. of concentrated hydrochloric acid, and extracted with three 100-ml. portions of benzene. All the organic layers are combined and dried over anhydrous sodium sulfate. Filtration and concentration of the solution with a rotary evaporator, followed by exposure to high vacuum for 2–3 hours, affords 17.3–19.3 g. of the crude product (Note 3). Low-boiling impurities are removed by vacuum distillation (Note 4), the residual oil (14–15 g.) is transferred to a 50-ml. flask equipped with a short-path distillation apparatus, and vacuum distillation is continued. A forerun is taken until no rise in boiling point is observed before 7.2–8.5 g. (23–27%) of dimethyl nitrosuccinate is collected as a colorless oil, b.p. 85° (0.07 mm.), n_D^{20} 1.4441 (Note 5).

2. Notes

1. *N,N*-dimethylacetamide was treated with molecular sieves for 2 days, decanted, and distilled under reduced pressure, b.p. 85° (30 mm.), before use.

2. Methyl nitroacetate was prepared by the method in *Org. Synth.*, **Coll. Vol. 6**, 797 (1988). It should be distilled before use.

3. GC analysis of the crude mixture (SE-30 on Chromosorb W, 1 m., 150°) showed the presence of some low-boiling materials (including unreacted methyl nitroacetate) and a significant amount of the doubly alkylated by-product, trimethyl 2-nitro-1,2,3-propanetricarboxylate.

4. The bath temperature should be maintained below 70–75°. Distillation was carried out using a Claisen head, and the receiving flasks were immersed in ice.

The checkers found it convenient to omit this distillation and the subsequent transfer. Instead the crude product was placed in a 25-ml. flask and carefully distilled (0.07 mm). The bath temperature was raised slowly, and a forerun was collected until the boiling point stabilized.

5. The distilled product was determined by the checkers to be 85–90% pure (GC analysis), the major impurity being the doubly alkylated by-product. Purity can be increased to 95% by redistillation. The

checkers found that conducting the experiment on a $\frac{3}{4}$ scale resulted in increased yield (34%) and purity (90–93%) of once-distilled product.

For twice-distilled material: IR (liquid film) cm^{-1} : 1745 strong, 1565 strong, 1430 medium strong; ^1H NMR (CDCl_3), δ (multiplicity, coupling constant J in Hz., number of protons): 3.14–3.45 (m, 2H), 3.76 (s, 3H), 3.86 (s, 3H), 5.6 (d of d, $J = 6$ and 8, 1H).

3. Discussion

Diethyl nitrosuccinate has been prepared by oxidation of diethyl nitrososuccinate,² and by the reaction of sodium nitrite with diethyl bromosuccinate, but in the latter case no experimental conditions were described.³

The present method is a simple, one-step procedure employing commercially available or readily accessible starting materials. Other α -nitro carboxylic esters may be prepared in this way;⁴ for example, dimethyl 2-nitropentanedioate was prepared in 45–50% yield.

References and Notes

1. School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan.
 2. J. Schmidt and K. Th. Widmann, *Ber. Dtsch. Chem. Ges.*, **42**, 497 (1909).
 3. R. Gelin and S. Gelin, *C.R. Hebd. Seances Acad. Sci.*, **256**, 3705 (1963).
 4. S. Zen and E. Kaji, *Bull. Chem. Soc. Jpn.*, **43**, 2277 (1970); E. Kaji and S. Zen, *Bull. Chem. Soc. Jpn.*, **46**, 337 (1973).
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

sodium methoxide (124-41-4)

N,N-dimethylacetamide (127-19-5)

Dimethyl nitrosuccinate,
Butanedioic acid, 2-nitro-, dimethyl ester (28081-31-4)

methyl bromoacetate (96-32-2)

Methyl nitroacetate (2483-57-0)

trimethyl 2-nitro-1,2,3-propanetricarboxylate

Diethyl nitrosuccinate

diethyl nitrososuccinate

diethyl bromosuccinate

dimethyl 2-nitropentanedioate