



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.

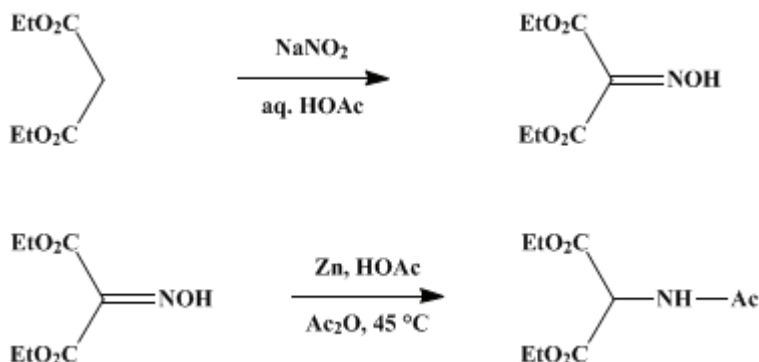
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 5, p.373 (1973); Vol. 40, p.21 (1960).*

## DIETHYL ACETAMIDOMALONATE

[Malonic acid, acetamido-, diethyl ester]



Submitted by Arthur J. Zambito and Eugene E. Howe<sup>1</sup>.  
Checked by John C. Sheehan and Alma M. Boston.

### 1. Procedure

A. *Diethyl isonitrosomalonnate*. In a 500-ml. three-necked, round-bottomed flask, equipped with a mechanical stirrer and thermometer, is placed 50 g. (47.4 ml., 0.312 mole) of *diethyl malonate*. The flask is cooled in an ice bath, and a mixture of 57 ml. of glacial *acetic acid* and 81 ml. of water is added with stirring. With the temperature at about 5°, a total of 65 g. of *sodium nitrite* (Note 1) (0.944 mole) is added in portions over a period of 1.5 hours, the temperature being maintained around 5° during the addition. After all the *sodium nitrite* is added, the ice bath is removed, and the stirring is continued for 4 hours (Note 2). During this time, the temperature reaches a maximum of 34–38° within 2 hours and falls to about 29° by the end of the stirring period. Gases which escape during the reaction (mostly oxides of nitrogen) are led to the hood.

The reaction mixture is transferred to a 300-ml. separatory funnel and is extracted with two 50-ml. portions of *ether*. The combined ethereal solution of *diethyl isonitrosomalonnate* is used in the next step immediately or, if desired, may be used after storage in a refrigerator overnight (Note 3).

B. *Diethyl acetamidomalonate*. The solution of *diethyl isonitrosomalonnate* described above, 86 g. (0.842 mole) of *acetic anhydride*, and 225 ml. (3.95 moles) of glacial *acetic acid* are placed in a 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a dropping funnel. With vigorous stirring 78.5 g. (1.20 moles) of *zinc* dust is added in small portions over a period of 1.5 hours in such a manner that the temperature of the reaction is maintained at 40–50°. The reaction is markedly exothermic during most of the *zinc* addition, and intermittent cooling (water bath) is required. After all the metal has been added, the mixture is stirred for an additional 30 minutes.

The reaction mixture is filtered with suction and the cake is washed thoroughly with two 200-ml. portions of glacial *acetic acid* (Note 4). The combined filtrate and washings are evaporated under reduced pressure on the steam bath until a thick oil, which generally partially crystallizes, remains. To purify the crude product, 100 ml. of water is added, and the flask is warmed on a steam bath until the solid melts. The mixture of water and oil is stirred rapidly in an ice bath, and *diethyl acetamidomalonate* crystallizes as a fine white product. After cooling in an ice bath for an additional hour, the product is collected by filtration, washed once with cold water, and dried in air at 50°. A second crop is obtained by concentrating the mother liquor under reduced pressure. The yield of *diethyl acetamidomalonate*, m.p. 95–97° (Note 5), is 52–53 g. (77–78%) based on malonic ester.

### 2. Notes

1. Owing to the instability of [sodium nitrite](#) solutions, the addition of the solid salt is preferred.
2. Prolonging the stirring to 24 hours has no effect on the yield of [diethyl acetamidomalonate](#).
3. No attempt has been made to purify [diethyl isonitrosomalonate](#). This product has been known to explode during distillation.
4. The [zinc](#) cake is very heavy and may be washed by slurring on a sintered-glass funnel or, if a standard Büchner funnel is used, by removing and slurring in a beaker.
5. The [diethyl acetamidomalonate](#) obtained is of high purity. If a product of inferior quality is obtained, it may be recrystallized from hot water, using 2.5 cc. per g. Upon cooling, the product separates first as an oil. With rapid stirring, it is converted to fine white crystals which are easily washed with cold water. [Diethyl acetamidomalonate](#) may be recrystallized in this manner with 97% recovery. The first crop amounts to 91% and the mother liquors may be concentrated to yield an additional 6%.

### 3. Discussion

[Diethyl acetamidomalonate](#) was first reported by Cherchez<sup>2</sup> in 1931, when in an attempt to carry out a carbon alkylation of [diethyl aminomalonate](#) with [acetyl chloride](#) he obtained a quantitative yield of [diethyl acetamidomalonate](#). This method of preparation, however, is not practical since [diethyl aminomalonate](#) is unstable and is made in relatively poor yields.

Snyder and Smith<sup>3</sup> prepared [diethyl acetamidomalonate](#) in 40% yield by reduction of [diethyl isonitrosomalonate](#) in [ethanol](#) over [palladium](#) on charcoal followed by direct acetylation of [diethyl aminomalonate](#) in the filtrate with [acetic anhydride](#). Ghosh and Dutta<sup>4</sup> used [zinc](#) dust instead of [palladium](#). A modification using [Raney nickel](#) is described by Akabori et al.<sup>5</sup> Shaw and Nolan<sup>6</sup> reported a 98% yield by conversion of diethyl oximinomalonate-sodium acetate complex.

#### 4. Use of [Diethyl Acetamidomalonate](#)

[Diethyl acetamidomalonate](#) is useful in the synthesis of  $\alpha$ -amino acids by alkylation, as, for example, [histidine](#) and [tryptophan](#).

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 5, 376](#)

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### References and Notes

1. Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Rahway, New Jersey.
2. V. Cherchez, *Bull. Soc. Chim.*, **49**, 45 (1931).
3. H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **66**, 350 (1944).
4. T. N. Ghosh and S. Dutta, *J. Indian Chem. Soc.*, **32**, 20 (1955).
5. S. Akabori et al., Japan pat. 274 (January 20, 1954).
6. K. N. F. Shaw and C. Nolan, *J. Org. Chem.*, **22**, 1668 (1957).

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### Appendix

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

oxides of nitrogen

diethyl oximinomalonate-sodium acetate complex

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

sodium nitrite (7632-00-0)

Raney nickel (7440-02-0)

zinc (7440-66-6)

palladium (7440-05-3)

diethyl malonate (105-53-3)

histidine (71-00-1)

tryptophan (73-22-3)

Diethyl acetamidomalonate,  
Malonic acid, acetamido-, diethyl ester (1068-90-2)

diethyl isonitrosomalonate (6829-41-0)

diethyl aminomalonate (6829-40-9)