A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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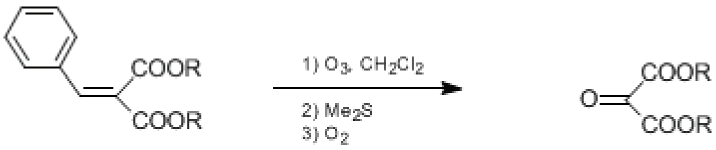
DIALKYL MESOXALATES BY OZONOLYSIS OF DIALKYL BENZALMALONATES: DIMETHYL MESOXALATE

[Propanedioic acid, oxo-, dimethyl ester]



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Checked by Makoto Kaino and Hisashi Yamamoto.

1. Procedure

Caution! Ozone is extremely toxic and can react explosively with certain oxidizable substances. Ozone also reacts with some compounds to form explosive and shock-sensitive products. Ozone should only be handled by individuals trained in its proper and safe use and all operations should be carried out in a well-ventilated fume hood behind a protective safety shield. [Note added September 2009].

A 300-mL wash bottle with an inlet tube fitted with a wide pore glass frit and equipped with a stirring bar is charged with 40.0 g (0.18 mol) of dimethyl benzalmalonate (Note 1) dissolved in 150 mL of dichloromethane. The cooled solution (0°C, ice bath) is purged with argon (10 min) and then a stream of ozone is passed through with vigorous stirring for 4.5 hr (Note 2). After the reaction is complete (TLC, silica gel, diethyl ether/petroleum ether = 1:1), excess ozone is removed by purging with argon (10 min) and 15 mL of dimethyl sulfide (Note 3) is slowly added at 0°C (ice bath). Stirring is continued for 1 hr at this temperature and 2 hr at ambient temperature. Finally, air is blown through the solution for 12 hr (Note 4) and the residue is distilled at 20 mm, boiling range 90–100°C (Note 5) to give a yellow liquid that is further purified by filtration through 150 g of silica gel (SiO_2) (Note 6) (elution with diethyl ether). The solvent is removed under reduced pressure and the residue is recrystallized from ethyl acetate to give 23.9 g (80%) of the dimethyl mesoxalate hydrate as colorless crystals (Note 7). Dehydration of the product is accomplished by azeotropic removal of water. The hydrate is dissolved in dichloromethane (150 mL) and heated for 12 hr in a Soxhlet apparatus (Note 8) equipped with a thimble containing layers of phosphorus pentoxide and basic alumina. The solvent is then evaporated and the residue distilled at reduced pressure to give 20.1 g (76%) of the ester as a yellow liquid [bp 94°C (20 mm)].

2. Notes

1. Dimethyl benzalmalonate and the corresponding esters of other alcohols can be prepared according to an Organic Syntheses procedure or as described in standard textbooks.[2] [3]
2. A Fischer Ozonizator 502 was used. The flow was adjusted to about 70 L/hr and the ozone content to 2–3 vol.%. The checkers used Japan Ozone Co. Ltd. 0–3–2 Ozonator. The flow was adjusted to about 1.3 mmol/min. Efficiency of stirring affects the yield greatly.
3. Dimethyl sulfide (Me_2S) was purchased from Tokyo Kasei; it is also available from Aldrich Chemical Company, Inc.
4. By this procedure the benzaldehyde is oxidized to benzoic acid, which is easily removed from the products.
5. Esters of higher alcohols may be filtered directly through silica gel and further purified by recrystallization.
6. Silica gel is 60 mesh.
7. All ester hydrates prepared were crystalline and can be stored without decomposition.
8. A 250-mL Soxhlet apparatus was used.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The method described is an improved procedure based on a work appearing in the patent literature.[4] Mesoxalates have been prepared by direct oxidation of malonates with selenium dioxide (SeO_2) or nitrogen dioxide (N_2O_4),[5,6,7] by thermolysis of brominated malonates,[8,9] or by oxidative cleavage of malonates with ozone[10,11] or singlet oxygen.[12] Diethyl mesoxalate is commercially available.

The procedure described has advantages over previously published methods. The starting material is easily obtained on a large scale at low cost. The ozonolysis can be conducted even on a large scale (150 g) and the workup is simple since the benzoic acid that is also formed can be removed by distillation, chromatography, or crystallization. The method is general and can be applied to different esters including chiral derivatives such as dimenthyl mesoxalate (see Table).

TABLE
PREPARATION OF DIALKYL MESOXALATES

	Ester Hydrate		
R	Yield [%]	m.p.°C (Solvent)	Ester b.p. [°C]
Me	77	76 (ethyl ether)	110/17 mm
i-Pr	70	56–57 (t-BuOMe/pet. ether)	96/10 mm
Benzyl	86	55–57 (t-BuOMe/pet. ether)	
(−) Menthyl	74	115 (Et_2O/pet. ether)	
(−)-Bornyl	42	93–95 (Et_2O/pet. ether)	

Mesoxalates are highly reactive substrates because of their strongly polarized carbon-oxygen bond. They have been used in pericyclic processes (e.g. Diels-Alder reactions,[13,14,15,16,17] ene reactions,[18,19] [3+2][20] and [2+2][21] cycloadditions), in aldol[22] and Wittig as well as Friedel-Crafts reactions.[23] Further applications arise from the use of the corresponding imines in hetero Diels-Alder reactions[24,25] and electrophilic cyclizations.[26,27,28,29,30]

References and Notes

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

alumina

silica gel

petroleum ether

ethyl acetate (141-78-6)

ethyl ether,
diethyl ether (60-29-7)

oxygen (7782-44-7)

Benzoic acid (65-85-0)

benzaldehyde (100-52-7)

selenium dioxide (7446-08-4)

nitrogen dioxide (10102-44-0)

dichloromethane (75-09-2)

ozone (10028-15-6)

dimethyl sulfide (75-18-3)

argon (7440-37-1)

phosphorus pentoxide (1314-56-3)

Dimethyl mesoxalate,
Propanedioic acid, oxo-, dimethyl ester (3298-40-6)

dimethyl benzalmalonate (6626-84-2)

dimethyl mesoxalate hydrate

Diethyl mesoxalate (609-09-6)

dimenthyl mesoxalate