Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

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METHYL DIFORMYLACETATE

[2-Propenoic acid, 2-formyl-3-hydroxy-, methyl ester]

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1. Procedure

A. *Potassium monomethyl malonate*. Dimethyl malonate ((Note 1), 264.2 g, 2.0 mol) is dissolved in anhydrous methanol ((Note 2), 1150 mL) contained in a dry, 3-L, one-necked flask containing a large magnetic stirring bar and protected from atmospheric moisture with a calcium sulfate-filled drying tube. The solution is stirred magnetically and cooled to ice-water bath temperature. Potassium hydroxide pellets (112.2 g 2.0 mol) are added rapidly to the cold solution and the reaction mixture is allowed to warm to room temperature with stirring overnight. The colorless crystals of potassium monomethyl malonate that form are recovered by suction filtration through a Büchner funnel and washed with anhydrous diethyl ether. The combined filtrate and diethyl ether wash are concentrated at 30°C to a volume of ca. 750 mL on a rotary evaporator. The resulting crystalline precipitate is recovered as before by filtration and washing and combined with the first crop of crystals to give 220 g (71%) of potassium monomethyl malonate as fine colorless needles, mp 204–207°C. These crystals are dried under vacuum (0.1 mm) before use in the following reaction.

B. *Methyl diformylacetate*. Freshly distilled phosphorus oxychloride (612 g, 4 mol) is added dropwise with constant stirring at ambient temperature (Note 3) to dimethylformamide (1460 g) contained in a 3-L, three-necked flask equipped with a mechanical paddle stirrer, immersion thermometer, and a 500-mL pressure-equalizing addition funnel fitted with a calcium chloride-filled drying tube. The reaction mixture warms up and turns to a dark reddish-brown color during addition of the phosphorus oxychloride and formation of the Vilsmeier reagent [$(CH_3)_2N^+$=CHCl Cl^-]. The addition funnel is replaced with a 10-in. long West condenser (Note 4), and then the reaction mixture is cooled to 0°C by immersing the reaction flask in an ice-salt water bath. The cooling bath is removed and potassium monomethyl malonate (206 g, 1.32 mol) is added to the stirred reaction mixture in ten equal portions over a 30 min period (Note 3) and (Note 5), keeping the temperature of the mixture below 90° C. The dark-brown mixture then is stirred and heated on a water bath at 90°C for 4 hr. Gas (CO_2 plus HCl) evolves initially from the reaction on heating (Note 6). The thermometer is replaced with a glass stopper, the condenser is fixed for distillation by addition of a distilling head and vacuum distillation receiver, and the reaction solvent is removed from the flask by distillation at ca. 2 mm on a steam bath (Note 7). The resulting dark-brown liquid is poured onto ice (4 kg, (Note 3)). A saturated aqueous solution of potassium carbonate (1.3 kg) is added slowly to the ice-cold crude reaction product with constant stirring until the pH of the mixture stabilizes at ca. 1 l. Considerable foaming and gas evolution (CO_2) occur during the addition of the base. The resulting basic solution is stirred magnetically at ambient temperature for 48 hr and then extracted with ethyl acetate in four 1-L portions. The organic phases are discarded, and the aqueous phase is saturated with potassium chloride (500 g) by stirring at ambient temperature until no more salt dissolves. This mixture is mixed with ice (1 kg), slowly acidified to pH 1 with ice-cold 12 *N* hydrochloric acid, and then thoroughly extracted with four 2-L portions of diethyl ether (Note 8). The combined cold ether extracts are washed with a saturated aqueous solution of potassium chloride (4 L) and dried over anhydrous sodium sulfate (500 g) for 1 hr. The solution is decanted from the desiccant, combined with a 500-mL diethyl ether wash of the desiccant, concentrated under reduced pressure to ca. 500 mL, and redried over anhydrous sodium sulfate. After removal of the desiccant by gravity filtration, the diethyl ether is removed by rotary evaporation at water aspirator

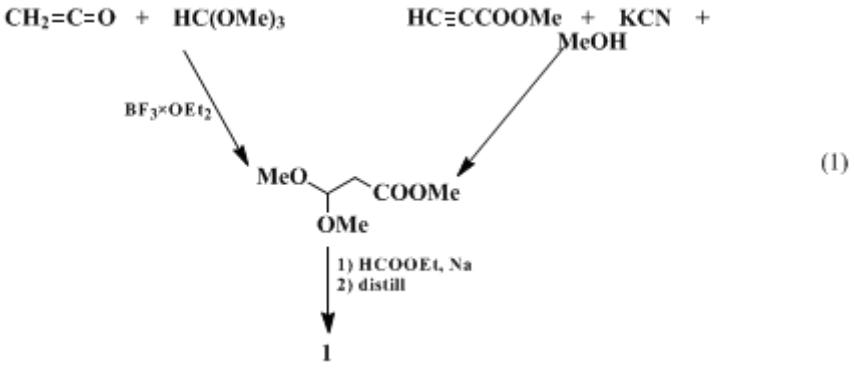
pressure and 25°C. Fractional distillation of the resulting liquid residue at 2 mm with a N_2 bleed capillary through a Claisen head first gives a little dimethylformamide. When dimethylformamide ceases to distill (Note 9), the receiver is cooled in a dry ice–ethanol bath and the methyl diformylacetate distilled at 58–61°C to give 86–94 g (50–55%) of a colorless, solid distillate, which melts at about 10°C (Note 10) and (Note 11). Methyl diformylacetate prepared in this way is stable for at least 6 months if stored at −20°C.

2. Notes

1. All reagents are used as received from commercial suppliers unless stated otherwise.
2. Reagent grade methanol is made anhydrous by refluxing over $Mg(OCH_3)_2$ according to the method of Vogel.[2]
3. All the following operations must be done in a hood.
4. The desiccant in the drying tube should be replaced with fresh calcium chloride and the drying tube fitted onto the top of the condenser.
5. The salt is added by replacing the condenser with a glass powder funnel, quickly pouring the crystalline solid through the funnel into the flask, and then replacing the powder funnel with the condenser.
6. The condenser can be cooled to prevent loss of solvent that is carried out of the reaction mixture by the escaping gases.
7. The volume of dimethylformamide distillate is ca. 1000 mL, and distillation is stopped when no more liquid distills from the reaction mixture.
8. The solvent extractions and washings should be done as rapidly as is possible since the crude methyl diformylacetate is not stable to small amounts of acid or base over long periods.
9. Dimethylformamide ceases to distill at a temperature less than 30°C.
10. Considerable product is lost if the receiver is not chilled to a low temperature.
11. The submitters have obtained the same yield when this procedure was done on scales from 0.5 to 1.3 mol.

3. Discussion

Methyl diformylacetate can be prepared from ketene and trimethyl orthoformate,[3] or methyl propiolate and methanol,[4] via formylation of the methyl 3,3-dimethoxypropanoate intermediate (equation 1). The present procedure is better because it avoids the tedious preparation of ketene,[3] affords a superior yield,[3] or is much cheaper[4] than the other two methods. A fourth method[5] for its preparation (equation 2) should permit the preparation of any ester of diformylacetic acid that is stable to Birch reduction and ozonolysis conditions. However, this method is not convenient for use above a 0.1-mol scale, nor recommended for reasons of safety because of the amount of an O_2/O_3, mixture needed at larger scales.



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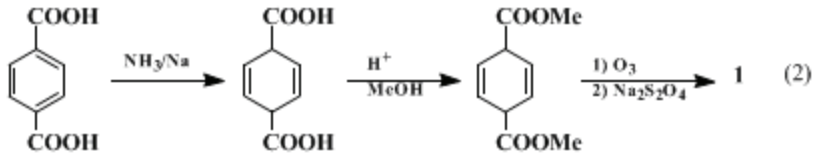

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 254

References and Notes

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

$Mg(OCH_3)_2$

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrochloric acid,
HCl (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

CO_2 (124-38-9)

Phosphorus Oxychloride (21295-50-1)

potassium hydroxide pellets (1310-58-3)

potassium chloride (7447-40-7)

dimethylformamide (68-12-2)

methyl propiolate (922-67-8)

trimethyl orthoformate (149-73-5)

dimethyl malonate (108-59-8)

Methyl diformylacetate

2-Propenoic acid, 2-formyl-3-hydroxy-, methyl ester (39947-70-1)

potassium monomethyl malonate (38330-80-2)

methyl 3,3-dimethoxypropanoate (7424-91-1)

diformylacetic acid