



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.

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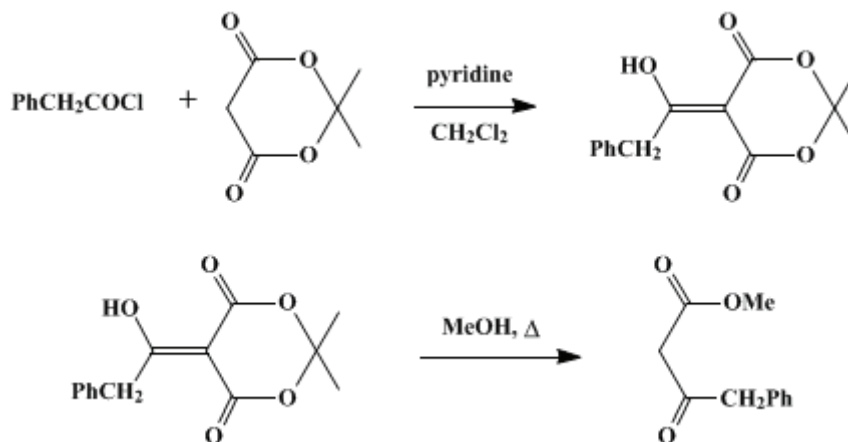
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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METHYL PHENYLACETYLACETATE FROM PHENYLACETYL CHLORIDE AND MELDRUM'S ACID

[Benzenebutanoic acid, β -oxo-, methyl ester]



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Checked by Michael J. Taschner, Hans P. Märki, and Clayton H. Heathcock.

1. Procedure

Into a 300-mL, round-bottomed flask equipped with a dropping funnel and a magnetic stirrer is placed a solution of 23.75 g (0.165 mol) of recrystallized [Meldrum's acid](#) ([Note 1](#)) in 65 mL of anhydrous [dichloromethane](#). The flask and its contents are cooled in an ice bath, and 32.5 mL (0.40 mol) of anhydrous [pyridine](#) ([Note 2](#)) is added with stirring under an [argon](#) atmosphere over a 10-min period. To the resulting colorless clear solution is added a solution of 25.0 g (0.16 mol) of freshly distilled [phenylacetyl chloride](#) ([Note 3](#)) in 50 mL of anhydrous [dichloromethane](#) over a 2-hr period. After the addition is complete, the resulting orange, cloudy reaction mixture is stirred for 1 hr at 0°C, then for an additional 1 hr at room temperature. The reaction mixture is diluted with 35 mL of [dichloromethane](#), and then poured into 100 mL of 2 *N* [hydrochloric acid](#) containing crushed ice. The organic phase is separated and the aqueous layer extracted twice with 25-mL portions of [dichloromethane](#). The organic phase and the extracts are combined, washed twice with 25-mL portions of 2 *N* [hydrochloric acid](#) and 30 mL of saturated [sodium chloride](#) solution, and dried over anhydrous [sodium sulfate](#). The solvent is removed with a rotary evaporator to yield an acyl Meldrum's acid ([Note 4](#)) as a pale-yellow solid.

The solid acyl Meldrum's acid, without purification, is refluxed in 250 mL of anhydrous [methanol](#) for 2.5 hr. The solvent is removed with a rotary evaporator, and the residual oil is distilled under reduced pressure to give 25.2 g (82%) of [methyl phenylacetylacetae](#) as a colorless liquid, bp 126–128°C/(0.6 mm).

2. Notes

1. [Meldrum's acid](#), 2,2-dimethyl-1,3-dioxane-4,6-dione, is available from the Aldrich Chemical Company, Inc. It may also be prepared from [malonic acid](#) and [acetone](#).² It is used in this preparation after recrystallization from [acetone](#) or from [acetone](#)–[hexane](#). The checkers found that a final product of significantly lower purity is obtained if the [Meldrum's acid](#) is not recrystallized.
2. The checkers used [pyridine](#) that had been distilled from [calcium hydride](#).
3. [Phenylacetyl chloride](#) is supplied by Wako Pure Industries, Ltd. (Japan) and the Aldrich Chemical Company, Inc. It is distilled before use, bp 95–96°C/(12 mm). The checkers found the distilled commercial material to be slightly pink. However, material of this quality gave a good yield of pure

product.

4. The product, 2,2-dimethyl-5-phenylacetyl-1,3-dioxane-4,6-dione, is isolated in its enol form in 97% yield. If desired, it may be further purified by recrystallization from ether–hexane to give pale-yellow prisms, mp 96–97°C (dec). The checkers recrystallized the material from dichloromethane–hexane and obtained 65% yield of material, mp 94–96°C (dec) and 7%, mp 84–90°C. The ¹H NMR spectrum of this compound has absorptions at δ 1.65 (s, 6 H), 4.30 (s, 2 H), 7.20 (s, 5 H), and 15.0 (br s, 1 H).

3. Discussion

Because β-keto esters are among the most important intermediates in organic synthesis, many methods have been developed for their synthesis.³ However, it is still desirable to have a general and practical method for preparation of β-keto esters of the general type RCOCH₂CO₂R', and thence by alkylation with alkyl halides compounds of the type RCOCHR"CO₂R'.⁴ The available synthetic methods can be classified broadly in three categories: those involving acetoacetic esters,⁵ those involving mixed malonic esters,⁶ and those involving malonic acid half esters.⁷ The procedure described herein⁸ may be classified as one of the malonic ester methods. The procedure consists of two simple steps and utilizes readily accessible starting materials. When the carboxylic acid chloride is not available, the carboxylic acid may be condensed with Meldrum's acid in the presence of a condensing agent such as ethyl phosphorocyanidate.⁹

Methanolysis or ethanolysis of an acyl Meldrum's acid is performed simply by refluxing in methanol or ethanol solution. The products are methyl or ethyl β-keto esters, and they can usually be purified by distillation. When a higher ester (such as benzyl, *tert*-butyl, or trichloroethyl) is required, it is easily prepared by refluxing the acyl Meldrum's acid in benzene containing about 3 equiv of the appropriate alcohol.

Recently, Melillo and co-workers applied this Meldrum's acid method with some modifications to the synthesis of thienamycin. A carboxylic acid was treated with carbonyldiimidazole, followed by treatment with Meldrum's acid to give an acyl Meldrum's acid, which was converted to a β-keto *p*-nitrobenzyl ester by refluxing in acetonitrile containing *p*-nitrobenzyl alcohol.¹⁰

References and Notes

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

ester

benzyl, tert-butyl, or trichloroethyl

acyl Meldrum's acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

acetone (67-64-1)

pyridine (110-86-1)

dichloromethane (75-09-2)

Malonic acid (141-82-2)

phenylacetyl chloride (103-80-0)

hexane (110-54-3)

argon (7440-37-1)

calcium hydride (7789-78-8)

CARBONYLDIIMIDAZOLE

p-Nitrobenzyl alcohol (619-73-8)

Methyl phenylacetylacetate,
Benzenebutanoic acid, β -oxo-, methyl ester (37779-49-0)

2,2-dimethyl-1,3-dioxane-4,6-dione,
MELDRUM'S ACID (2033-24-1)

2,2-Dimethyl-5-phenylacetyl-1,3-dioxane-4,6-dione

dichloromethanehexane

ethyl phosphorocyanidate