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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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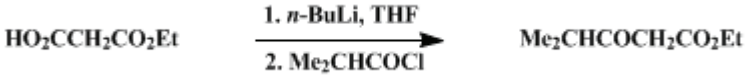
ALIPHATIC AND AROMATIC β-KETO ESTERS FROM MONOETHYL MALONATE: ETHYL 2-BUTYRYLACETATE

[Pentanoic acid, 4-methyl-3-oxo-, ethyl ester]



Submitted by W. Wierenga and H. I. Skulnick[1].
Checked by Stefan Blarer, Daniel Wasmuth, and Dieter Seebach.

1. Procedure

Ethyl 2-butyrylacetate. In a 1-L, three-necked, round-bottomed flask fitted with a mechanical stirrer, dry nitrogen inlet, and thermometer is placed 19.8 g (0.150 mol) of monoethyl malonate (Note 1), 350 mL of dry tetrahydrofuran (THF, (Note 2)), and 5 mg of 2,2'-bipyridyl. The solution is cooled to approximately −70°C (in an isopropyl alcohol-dry ice bath) and a 1.6 *M* solution of butyllithium in hexane is added from a dropping funnel while the temperature is allowed to rise to approximately −10° C. Sufficient butyllithium is added (approx. 190 mL) until a pink color persists for several minutes (Note 3). The heterogeneous solution is recooled to −65°C and 7.90 mL (7.98 g, 75 mmol) of isobutyryl chloride (Note 4) is added dropwise over 5 min. The reaction solution is stirred for another 5 min (Note 5) and then poured into a separatory funnel containing 500 mL of ether and 300 mL of cold, 1 *N* hydrochloric acid (Note 6). The funnel is shaken, the layers are separated, and the organic phase is washed with two 150-mL portions of saturated aqueous sodium bicarbonate, followed by 150 mL of water, and dried over anhydrous sodium sulfate. Removal of the solvents under reduced pressure leaves 11.70 g (98%) of ethyl 2-butyrylacetate (Note 7). The crude product can be distilled at 70–74°C (7 mm) (80% yield, 96% purity by GLC).

2. Notes

1. The potassium salt of monoethyl malonate, available from the Aldrich Chemical Company, Inc., can be used after neutralization. Direct use of the potassium salt with only 1 equiv. of butyllithium gave substantially lower yields. Alternatively, monoethyl malonate can be conveniently prepared in high yield from diethyl malonate.[2]
2. For smaller-scale reactions, THF was dried and used directly by distillation from sodium–benzophenone, or first from KOH and then from $LiAlH_4$. The checkers used only dry THF for the present, large-scale procedure as well.
3. Initially, butyllithium can be added rapidly (20 mL/min) while the cooling bath is removed. A slightly exothermic reaction is noted. Toward the end of the reaction, dropwise addition should be used; the pink color will form and then dissipate. The checkers found it more convenient to use the calculated amount of a freshly titrated[3] solution of butyllithium.
4. Isobutyryl chloride was used as purchased from Aldrich Chemical Company, Inc. or Fluka AG.

TABLE I
REACTION OF ACID CHLORIDES WITH DILITHIO MONOETHYL MALONATE

$RCOCl \rightarrow RCOCH_2CO_2C_2H_5$ R	Reaction Time (min)/ Temperature (°C)	Yield (%)[a]
$CH_3CH_2CH_2$	5/−65	95
$PhCH_2$	5/−65	99
Ph	30/−65	97
4-$CH_3OC_6H_4$	60/−65	90
4-ClC_6H_4	30/−65	96

2-ClC_6H_4	30/−65	95
2-$C_{10}H_7$	30/−65	95
3-Furyl	15/−65, 60 to 0	97
2-Pyrazinyl	15/−65, 60 to 0	91

[a]The purity of all products isolated is higher than 90% as determined by GLC or ^1H NMR. The only contaminants appear to be hydrocarbons including *n*-octane.

5. Reaction times and temperatures vary, depending on the substrate acid chloride (see Table 1).
6. For acid chlorides that contain a basic nitrogen, the aqueous phase is adjusted to approximately pH 7 by limiting the concentration of the hydrochloric acid.
7. Gas chromatographic analysis using a 3-ft, 3% OV-17 column at 90°C indicated a purity of 92% (retention time was 3.2 min) with GC-mass spectrometric identification showing M^+ *m/e* 158 (27%) and the base peak (100%) at *m/e* 113 ($C_6H_9O_2$). The ^1H NMR spectrum of undistilled material indicates impurities with resonances in the aliphatic region (δ: 1.5–1.0). The checkers recommend distillation of the crude product.

3. Discussion

Since the β-keto ester group is often a key moiety in organic syntheses, a general and efficient route to these 1,3-dicarbonyl compounds is highly desirable. We feel that the one-pot preparation from monoethyl malonate described here[4] represents an attractive alternative to previous methods[5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22] because of the following characteristics: (1) the reaction is general, as demonstrated by the diversity of examples in Table I; (2) the starting materials, (monoethyl malonate and the acid chlorides) are readily available and inexpensive; (3) the yields are high and therefore omission of purification is possible in many instances; and finally (4) the reaction is simple and easy to scale up.

The optimum ratio for high yields of β-ketoester is 1.7 (monoethyl malonate: acid chloride). A nonstoichiometric reaction for optimum yield is not a serious drawback in this case since the reagent in excess is the inexpensive dilithio monoethyl malonate. Our results show that lowering the ratio also lowers the yield, whereas an increase in the ratio beyond 1.7 has little effect.

References and Notes

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

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

KOH (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

diethyl malonate (105-53-3)

monoethyl malonate (1071-46-1)

isobutyryl chloride (79-30-1)

butyllithium (109-72-8)

Tetrahydrofuran,
THF (109-99-9)

$LiAlH_4$ (16853-85-3)

n-octane (111-65-9)

hexane (110-54-3)

potassium salt of monoethyl malonate (6148-64-7)

2,2'-bipyridyl (366-18-7)

Ethyl 2-butyrylacetate (3249-68-1)

Pentanoic acid, 4-methyl-3-oxo-, ethyl ester (7152-15-0)

3-Furyl

dilithio monoethyl malonate