[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

A New Synthesis of β-Keto Esters of the Type $RCOCH_2COOC_2H_5$[1,2]

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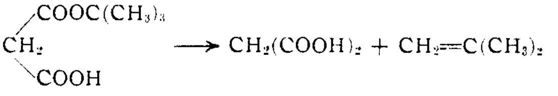
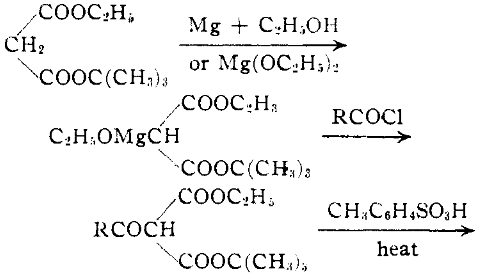
Various methods for synthesizing β-keto esters of the type $RCOCH_2COOC_2H_5$ are known.[3] However, none has been general and none has been entirely satisfactory for the preparation of certain β-keto esters of this type. The present paper describes a new method that appears to be quite general and which has been found satisfactory for the synthesis of certain β-keto esters that have been rather difficult to prepare by the common methods.

Our new method is based on the discovery that, in contrast to ethyl hydrogen malonate, which undergoes the common decarboxylation reaction on heating, *t*-butyl hydrogen malonate undergoes instead the elimination reaction to form isobutylene and malonic acid.[4] Since the remarkable ease with which this elimination reaction occurs is presumably due to an acid catalysis, it was reasonable to expect that a similar elimination involving the *t*-butyl ester group would occur with an acylated ethyl *t*-butyl malonate in the presence of acid to form isobutylene and the half-acid ethyl ester, which would decarboxylate to give a β-keto ester. This expectation has been realized. The reactions, including the acylation of ethyl *t*-butyl malonate with an acid chloride, may be represented by the following transformation.



$$CH_2\begin{cases}COOC(CH_3)_3\\COOH\end{cases} \longrightarrow CH_2(COOH)_2 + CH_2{=}C(CH_3)_2$$



$$CH_2\begin{cases}COOC_2H_5\\COOC(CH_3)_3\end{cases} \xrightarrow[\text{or } Mg(OC_2H_5)_2]{Mg + C_2H_5OH} C_2H_5OMgCH\begin{cases}COOC_2H_5\\COOC(CH_3)_3\end{cases} \xrightarrow{RCOCl} RCOCH\begin{cases}COOC_2H_5\\COOC(CH_3)_3\end{cases} \xrightarrow[\text{heat}]{CH_3C_6H_4SO_3H} RCOCH_2COOC_2H_5 + CH_2{=}C(CH_3)_2 + CO_2$$

Ethyl *t*-butyl malonate was converted into its magnesium derivative, which was acylated with an appropriate acid chloride.[5] The elimination reaction and decarboxylation of the crude acylated malonic ester was carried out in the presence of a catalytic amount of toluene sulfonic acid. The yields of the β-keto esters, calculated from ethyl *t*-butyl malonate, and the boiling points of the products on which these yields are based are given in Table I.

TABLE I

PREPARATION OF $RCOCH_2COOC_2H_5$ FROM ETHYL *t*-BUTYL MALONATE

R =	Method	B. p. °C.	Mm.	Yield, %
Ethyl[a]	A, B	88–93	17	63
Cyclohexyl[b]	A	146–150	18	65
2-Furyl[c]	B	137–139	9.5	70
Benzyl[d]	A	154–156	9	47
$CH_3CH{=}CH—$[e]	A	101–105	15	35

[a] Copper salt, m. p. 143–144°.[6] [b] 1-Phenyl-3-cyclohexyl-5-pyrazolone, m. p. 125–126°.[7] [c] 1-Phenyl-3-furyl-5-pyrazolone, m. p. 178–179°.[8] [d] 3-Benzyl-5-pyrazolone, m. p. 196–197°.[9] [e] Copper salt, m. p. 159°. Calcd. for $(C_8H_{11}O_3)_2Cu$: Cu, 17.0. Found: Cu, 16.5.

The magnesium derivative of ethyl *t*-butyl malonate was generally prepared by means of magnesium and alcohol (Method A). Since an ester interchange was possible using this method, the reaction was carried out using previously prepared magnesium ethoxide (Method B). The possibility of exchange is much less in the latter case; the amount of alcohol present is a minimum and the reaction time is much shorter. However, the two methods appear to be about equivalent.[9a] An appreciable amount of high-boiling material was obtained in every case but the products were fairly pure and could be further purified by redistillation.

The yields given in the table for ethyl propionylacetate, ethyl hexahydrobenzoylacetate and ethyl γ-phenylacetoacetate are somewhat higher than those that have been reported for these β-keto esters by other methods. Ethyl crotonylacetate is a new compound, while ethyl furoylacetate may be prepared readily by the condensation of ethyl furoate with ethyl acetate. We believe the method would probably be satisfactory for various β-keto esters of the type $RCOCH_2COOC_2H_5$, but

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[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

[2] Presented before the Organic Division of the American Chemical Society at the Cleveland meeting, April 3–7, 1944.

[3] See especially Hauser and Hudson, "Organic Reactions," Roger Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. 1, pp. 297–300.

[4] Baumgarten and Hauser, THIS JOURNAL, **66**, 1037 (1944).

[5] The analogous reaction with diethyl malonate has been carried out by Lund, *Ber.*, **67B**, 935 (1934).

[6] Dupont, *Compt. rend.*, **148**, 1524 (1909).

[7] Wahl and Meyer, *Bull. soc. chim.*, [4] **3**, 962 (1908).

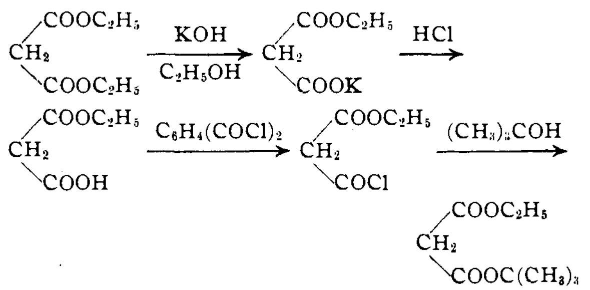
[8] Torrey and Zanetti, *Am. Chem. J.*, **44**, 416 (1910).

[9] Sonn and Litten, *Ber.*, **66B**, 1515 (1933).

[9a] ADDED IN PROOF.—Further work has now shown that Method B is probably to be preferred. When the preparation of ethyl propionylacetate was carried out by Method A on a larger scale than that reported, a large amount of higher-boiling material, shown to be diethyl propionylmalonate formed by ester exchange, was obtained. However, when Method B was used on a 0.35 mole scale, the yield of ethyl propionylacetate was essentially the same as that reported in Table I.

it is limited by the fact that ethyl *t*-butyl malonate is not commercially available.

In the present investigation ethyl *t*-butyl malonate was prepared from diethyl malonate by the series of reactions



Diethyl malonate was readily converted into the monopotassium salt of ethyl hydrogen malonate in about an 80% yield on a large scale, the reaction being a modification of the small scale preparation of Marguery.[10] The free acid, which was obtained from the salt in almost quantitative yield, was converted by phthalyl chloride into the corresponding acid chloride in yields of 75–80% by a modification of the general procedure of Kyrides.[11] The method was found to be superior to the action of thionyl chloride on either the acid[10] or the monopotassium salt.[12] Ethyl *t*-butyl malonate was prepared from the acid chloride in 85–90% yield according to the general procedure for preparing *t*-butyl esters.[13] The over-all yield of ethyl *t*-butyl malonate was 48–55%.

The new synthesis is also applicable to the direct preparation of substituted β-keto esters of the type $RCOCHR'COOC_2H_5$ and in certain cases the method would probably be preferred to the more common method of alkylating the requisite β-keto ester. We have prepared ethyl α-*n*-butylbenzoylacetate starting from diethyl *n*-butylmalonate by this method. The reactions were carried out essentially as described above, with the modification that thionyl chloride rather than phthalyl chloride was used to prepare the acid chloride. The over-all yield of ethyl *t*-butyl *n*-butylmalonate based on diethyl *n*-butyl malonate was 57%, ethyl α-*n*-butylbenzoylacetate being obtained from this compound in 48% yield.

An attempt to prepare certain β-keto esters directly from diethyl malonate without first preparing ethyl *t*-butyl malonate failed. Bernhard[14] reported that benzoylmalonic ester decomposed smoothly on steam-distillation into benzoylacetic ester, but we have found that the reaction goes in poor yield and that it cannot be applied to aliphatic compounds.

Experimental[15,16]

Ethyl *t*-Butyl Malonate.—In a five-liter three-necked flask equipped with a mercury-sealed stirrer, reflux condenser and dropping funnel were placed 400 g. (2.5 moles) of diethyl malonate (practical grade, dried over Drierite) and 1600 ml. of commercial absolute ethanol. To this was added with stirring during one hour a solution of 140 g. of potassium hydroxide in 1600 ml. of commercial absolute ethanol. A white crystalline precipitate formed. After stirring for three hours and standing overnight the mixture was heated to boiling and the solution filtered hot to remove dipotassium malonate. The monopotassium salt, which precipitated on cooling the filtrate, was filtered off, washed with a small amount of ether and dried *in vacuo*. Concentration of the mother liquor to about 500 ml. yielded another crop of crystals. The total yield of the monopotassium salt of ethyl hydrogen malonate was 350 g. (82%).

To a chilled solution of the potassium salt (106 g., 0.625 mole) in 60 ml. of water (immersed in an ice-bath) was added slowly with stirring 55 ml. of concentrated hydrochloric acid. The mixture was extracted three or four times with ether, the ethereal solution dried over sodium sulfate and the solvent distilled. The liquid residue of ethyl hydrogen malonate was dried *in vacuo* (2 mm.) at room temperature for three hours; yield, 79 g. (96%).

In a 500-ml. round-bottomed flask connected by means of a ground-glass joint to a three-way adapter, equipped with a mercury-sealed stirrer, dropping funnel and reflux condenser having a drying tube, was placed 240 g. (1.18 moles) of phthalyl chloride (Eastman Kodak Co. practical grade). Ethyl hydrogen malonate (124 g., 0.94 mole) was placed in the dropping funnel and the flask immersed in an oil-bath which was heated to 100–110°. The ethyl hydrogen malonate was added with stirring during thirty minutes. A vigorous evolution of hydrogen chloride took place. The stirring and heating were continued for two hours and the mixture then cooled. The three-way adapter was replaced by a 15-cm. Vigreux column and the mixture distilled at 20–25 mm. (water aspirator), collecting everything up to 90° (bath temperature up to 165°). Most of the distillate consisted of ethyl malonyl chloride, b. p. 83° at 22 mm.[17]; yield, 106 g. (75%).

In a one-liter three-necked flask equipped with a mercury-sealed stirrer, reflux condenser and dropping funnel were placed 81.4 g. (1.10 moles) of *t*-butyl alcohol (Eastman Kodak Co., dried over anhydrous potassium carbonate; b. p. 81.5–82.0°), 133 g. (1.10 moles) of dimethylaniline (Eastman Kodak Co., dried over potassium hydroxide; b. p. 91–92° at 25 mm.) and 200 ml. of anhydrous ether. The stirred solution was heated to refluxing, the flame removed and 161 g. (1.07 moles) of ethyl malonyl chloride in 100 ml. of anhydrous ether slowly added. At the end of the addition dimethylaniline hydrochloride crystallized, the mixture refluxing violently. After the reaction had subsided the mixture was stirred and refluxed for three hours and allowed to stand overnight. Water (150 ml.) was added to dissolve the dimethylaniline hydrochloride and the two layers separated. The aqueous phase was extracted once with ether and the combined ether layers were extracted with 50-ml. portions of 10% sulfuric acid until no cloudiness was observed in the extract when it was made alkaline. The ether phase was washed once with saturated sodium bicarbonate, dried over sodium sulfate followed by Drierite and the solvent distilled. The residue was distilled through a 15-cm. Vigreux column, yielding ethyl *t*-butyl malonate, b. p. 98–99° at 17 mm.[18]; yield, 183 g. (91%).

The over-all yield of ethyl *t*-butyl malonate from diethyl malonate for several runs was 48–55%.

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(10) Marguery, *Bull. soc. chim.*, [3] **33**, 541 (1905).

(11) Kyrides, THIS JOURNAL, **59**, 206 (1937).

(12) Staudinger and Becker, *Ber.*, **50**, 1023 (1917).

(13) Norris and Rigby, THIS JOURNAL, **54**, 2097 (1932); Abramovitch, Shivers, Hudson and Hauser, *ibid.*, **65**, 986 (1943).

(14) Bernhard, *Ann.*, **282**, 166 (1894).

(15) Microanalyses by Dr. T. S. Ma, Department of Chemistry, University of Chicago, Chicago, Illinois.

(16) Melting points are corrected, boiling points are uncorrected.

(17) Marguery[10] gives the boiling point as 71° at 15 mm.

(18) Hauser, Abramovitch and Adams [THIS JOURNAL, **64**, 2714 (1942)] give 93–95° at 17 mm. as the boiling point.

Ethyl Propionylacetate (Method A).—To 5.6 g. (0.23 mole) of magnesium turnings contained in a 500-ml. round-bottomed flask equipped with a reflux condenser were added 0.5 ml. of carbon tetrachloride and 5 ml. of absolute ethanol. After a few minutes a vigorous reaction started. The flask was cooled and 75 ml. of anhydrous ether was added through the condenser from a dropping funnel. To the mixture was added slowly 43.3 g. (0.23 mole) of ethyl *t*-butyl malonate in 20 ml. of absolute ethanol, the reaction mixture refluxing during the addition. The condenser was rinsed with an additional 50 ml. of anhydrous ether and the reaction mixture was refluxed for three hours. Most of the magnesium had dissolved and a white precipitate was present. To the mixture was added slowly 21.7 g. (0.235 mole) of propionyl chloride (Eastman Kodak Co.) dissolved in 25 ml. of anhydrous ether. The reaction mixture was then refluxed for a half-hour, the resulting solution, which was clear and contained only traces of unreacted magnesium, was chilled and 25 ml. of water was added. The mixture was acidified with dilute sulfuric acid and the ether phase, with which was combined an ether extraction of the aqueous phase, was dried over sodium sulfate followed by Drierite; the solvent was distilled at room temperature, leaving a residue of crude ethyl *t*-butyl propionylmalonate.

A solution of the crude ester in 100 ml. of dry benzene was placed in a 500-ml. flask equipped with a water eliminator[19] and the solution was refluxed to remove the last traces of water. One gram of toluenesulfonic acid was added and the solution refluxed again. A vigorous evolution of gas took place, the heating being continued until no more gas was evolved (one and one-half hours). The benzene solution was cooled, extracted with saturated sodium bicarbonate solution, dried over sodium sulfate followed by Drierite and the solvent distilled at atmospheric pressure. The residue was distilled through a 10-cm. Vigreux column, yielding 2.8 g. of forerun, b. p. 70–88° at 17 mm., and 19.7 g. (60%) of ethyl propionylacetate, b. p. 88–93° at 17 mm. A large higher-boiling residue remained in the distilling flask. From the forerun there was isolated in the form of its copper salt (m. p. 141–143°, on recrystallization from ligroin m. p. 143–144°[6]) an additional 1.0 g. of ethyl propionylacetate; total yield, 63%. The ethyl propionylacetate dissolved completely in 5% sodium hydroxide, showing the absence of any appreciable amount of malonic ester.

Ethyl Furoylacetate (Method B).—Magnesium ethoxide was prepared from magnesium, absolute ethanol and dry xylene according to Meerwein and Schmidt,[20] except that a small amount of carbon tetrachloride was used to initiate the reaction instead of mercuric chloride plus iodine. The excess alcohol and xylene were distilled and the magnesium ethoxide was dried on a steam-bath *in vacuo*.

In a 500-ml. three-necked flask equipped with a mercury-sealed stirrer, reflux condenser and dropping funnel were placed 11.4 g. (0.10 mole) of magnesium ethoxide and 75 ml. of anhydrous ether. Ethyl *t*-butyl malonate (18.8 g., 0.10 mole) was added with stirring and the mixture refluxed for fifteen minutes. Most of the magnesium ethoxide dissolved, a cloudy solution being formed. To this was added 14.4 g. (0.11 mole) of furoyl chloride (Eastman Kodak Co.) dissolved in 25 ml. of anhydrous ether. The solution refluxed vigorously, a precipitate forming toward the end of the addition. The reaction mixture was then refluxed for fifteen minutes. The crude ethyl *t*-butyl furoylmalonate was isolated and treated as described above for the corresponding propionyl ester. After distilling the solvent the residue was distilled through a 10-cm. Vigreux column at 10 mm., yielding 2.5 g. of material boiling at 65–136° and 13.9 g. boiling at 136–145°. On redistillation the second fraction gave 12.8 g. (70%) of ethyl furoylacetate, b. p. 137–139° at 10 mm.

Ethyl *t*-Butyl *n*-Butylmalonate.—Diethyl *n*-butylmalonate[21] (152 g., 0.7 mole) was dissolved in 450 ml. of commercial absolute ethanol and a solution of 39 g. of potassium hydroxide in 450 ml. of ethanol added. After stirring for three hours and standing overnight, the reaction mixture was heated to refluxing and filtered. The filtrate remained clear on cooling and was therefore evaporated to dryness *in vacuo*. The soapy residue was suspended in ether, chilled and treated with 200 ml. of cold 9 *M* sulfuric acid. The ether phase was separated, dried over sodium sulfate followed by Drierite and the solvent distilled, leaving a residue of ethyl hydrogen *n*-butylmalonate. The crude acid was dissolved in 250 ml. of dry benzene and 75 ml. of thionyl chloride was added. The reaction mixture was allowed to stand twelve hours at room temperature and was then heated twelve hours at 50–60° followed by thirty-six hours at 60–70°. The solvent was distilled *in vacuo* and the residue distilled from a modified Claisen flask, yielding 103 g. (71% based on diethyl *n*-butylmalonate) of ethyl *n*-butylmalonyl chloride, b. p. 90–107° at 9.5 mm.

Ethyl *t*-butyl *n*-butylmalonate (b. p. 126–128° at 15 mm.) was prepared from the acid chloride according to the preparation of ethyl *t*-butyl malonate given above; yield, 81%.

Ethyl α-*n*-Butylbenzoylacetate.—The reaction was carried out according to Method B, starting with 24.4 g. (0.10 mole) of ethyl *t*-butyl *n*-butylmalonate, 12.5 g. (0.11 mole) of magnesium ethoxide and 15.5 g. (0.11 mole) of benzoyl chloride. The compound was distilled through a 10-cm. Vigreux column at 5 mm., yielding 7.4 g. of forerun, b. p. 68–153°, and 14.8 g. of material boiling at 153–163°. Redistillation of the second fraction gave 11.8 g. (48%) of ethyl α-*n*-butylbenzoylacetate, b. p. 157–161° at 5 mm. A mid-fraction was analyzed.

Calcd. for $C_{15}H_{20}O_3$: C, 72.57; H, 8.12. Found: C, 72.43; H, 7.69.

The β-keto ester readily formed an amide when an alcoholic solution was allowed to stand with liquid ammonia for several days at room temperature; m. p. 153–154° (after recrystallization from dilute alcohol).

Anal. Calcd. for $C_{13}H_{17}O_2N$: N, 6.39. Found: N, 6.53.

Ethyl Benzoylacetate.—Diethyl benzoylmalonate[5] (28.2 g., 0.11 mole) was steam-distilled from a solution containing a small amount of sulfuric acid. The distillate was neutralized with sodium bicarbonate, extracted with ether, the ether solution dried over sodium sulfate followed by Drierite and the solvent distilled. The residue was distilled through a 20-cm. Vigreux column, yielding, in addition to considerable amounts of other material, 5.8 g. (27%) of ethyl benzoylacetate, b. p. 114–116° at 2 mm. (copper salt, m. p. 182–183°[22]).

A similar experiment using diethyl propionylmalonate[5] yielded only 7% of ethyl propionylacetate in the form of its copper salt.

Summary

1. A new synthesis of β-keto esters of the type $RCOCH_2COOC_2H_5$ has been developed, starting from ethyl *t*-butyl malonate.

2. Ethyl propionylacetate, ethyl hexahydrobenzoylacetate, ethyl furoylacetate, ethyl γ-phenylacetoacetate and ethyl crotonylacetate have been synthesized. This shows the generality of the method.

3. The synthesis of ethyl *t*-butyl malonate on a fairly large scale is described.

4. Ethyl α-*n*-butylbenzoylacetate has been synthesized in order to show the possibility of applying the method to other types of β-keto esters.

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[19] Dean and Stark, *J. Ind. Eng. Chem.*, **12**, 486 (1920).

[20] Meerwein and Schmidt, *Ann.*, **444**, 236 (1925).

[21] "Organic Syntheses," Col. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 250.

[22] Wislicenus, *Ber.*, **31**, 3157 (1898).