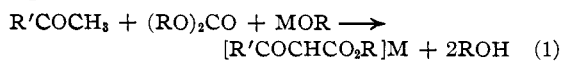


[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MALLINCKRODT CHEMICAL WORKS]

Alkyl Carbonates in Synthetic Chemistry. II. Condensation with Ketones. Synthesis of β -Keto Esters¹

BY V. H. WALLINGFORD, AUGUST H. HOMEYER AND DAVID M. JONES

The condensation of alkyl carbonates with organic esters described in a recent paper² affords a rather general method for preparing malonic esters. Similarly, alkyl carbonates may be condensed with ketones to produce β -keto esters. The general reaction is illustrated by equation (1)



but is not limited to methyl ketones.

In 1887, Claisen³ condensed acetophenone with diethyl carbonate by adding alcohol-free sodium ethylate slowly to the mixture without a solvent. Ethyl benzoylacetate was isolated in poor yield and was accompanied by high boiling by-products. Many years later Schroeter⁴ obtained about a 25% yield of methyl α,γ -diphenylacetoacetate by condensing dimethyl carbonate with dibenzyl ketone in ether by means of metallic sodium. Lux⁵ obtained ethyl acetoacetate in 40% yield by slowly adding acetone to a refluxing mixture of ether, diethyl carbonate and powdered sodium. Using metallic sodium or potassium in the presence of xylene or other solvent, Preobrashenski, Schtschukina and Lapina⁶ condensed dimethyl and diethyl carbonate with tropinone. The yields of tropinonecarboxylic esters were 70–80%. Although the investigations which have come to our attention have been moderately successful in isolated cases, they have not indicated a procedure generally applicable for the introduction of carbalkoxyl groups into ketones.

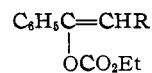
The procedure described in the present paper has been applied successfully to a variety of ketones as shown in Table I. The method is of considerable use in organic syntheses since the β -keto esters produced by the reaction are one of the most reactive classes of organic compounds. The method consists in heating or digesting the ketone with sodium or potassium alcoholate in a

large excess of the alkyl carbonate. The yields are improved if the alcohol concentration is maintained as low as possible by fractionating from the mixture both the alcohol introduced with the metal alcoholate and that produced by the reaction. The β -keto ester produced is present in the reaction mixture as the metal derivative and may be subjected directly to further reaction such as alkylation. The yields given in Table I probably do not represent the highest obtainable under optimum conditions.

Although the method is usually a suitable preparative procedure, certain exceptions may be noted. Ketones which are so active that they condense with themselves or polymerize rapidly under the conditions of the procedure give unsatisfactory yields of the β -keto esters. Examples are benzalacetone, acetone, methyl ethyl ketone, and mesityl oxide. Doubtless here, also, some carbalkoxylation occurs but the products are complex and difficult to separate. On the other hand, we have encountered ketones such as camphor and diisobutyl ketone which are too sluggish in reaction to work well in the procedure. The reaction of metal alcoholates with alkyl carbonates to form ethers and metal alkyl carbonates increases in rate rapidly at temperatures above about 100° limiting the extent to which one may force the carbalkoxylation. In the carbalkoxylation of propiophenone and butyrophenone, there were isolated in addition to the expected β -keto esters (I), the carbonic esters of the enol forms of the ketones (II).



I



II

Compounds of type II were also obtained by Haller and Bauer⁷ by the action of sodium and ethyl chlorocarbonate on these ketones. If we regard the alkyl carbonate as an acylating agent, compound I results from carbon acylation while compound II is the product of oxygen acylation. In the case of cyclohexanone the only product obtained was a compound of type II in 20% yield.

The authors wish to express their appreciation

(7) Haller and Bauer, *Compt. rend.*, **152**, 551 (1911).

(1) Presented before the Division of Organic Chemistry at the St. Louis Meeting of the American Chemical Society, April 8, 1941.

(2) Wallingford, Homeyer and Jones, *THIS JOURNAL*, **63**, 2056 (1941).

(3) Claisen, *Ber.*, **20**, 656 (1887).

(4) Schroeter, *ibid.*, **49**, 2712 (1916).

(5) Lux, *ibid.*, **62**, 1826 (1929).

(6) Preobrashenski, Schtschukina and Lapina, *ibid.*, **69**, 1615 (1936).

TABLE I
 CONDENSATION OF ALKYL CARBONATES WITH KETONES. SYNTHESIS OF BETA-KETO ESTERS

Starting material	Method	Product	Yield, %	B. p., °C., uncorr.	Mm.	M. p., °C., uncorr.	n_D	t , °C.
Diethyl ketone	A	Ethyl β -keto- α -methylvalerate ^b	20	103-106	32		1.419	24
Methyl isopropyl ketone	C	Me and Et β -keto- γ -methylvalerate ^a	Poor	70-81	10			
Methyl <i>t</i> -butyl ketone	C	Me and Et β -keto- γ , γ -dimethylvalerate ^d	Poor	ca-90	15			
Methyl isobutyl ketone	A	Ethyl β -keto- δ -methylcaproate ^e	60	96-98	14		1.4270	24
Methyl <i>n</i> -amyl ketone	B ^a	Ethyl β -keto-caprylate ^f	65	75-78	2		1.4337	20
Di- <i>n</i> -propyl ketone	A	Ethyl β -keto- α -ethylcaproate ^g	45	126-127	34		1.4225	31
Methyl neopentyl ketone	A	Ethyl β -keto- δ , δ -dimethylcaproate ^h	66	104-105	15		1.4334	24
Methyl <i>n</i> -hexyl ketone	B ^h	<i>n</i> -Propyl β -keto-pelargonate ^{c,i}	74	99-104	2		1.4373	21
Acetophenone	A	Ethyl benzoylacetate ^j	60	138-140	6		1.526	24
Acetophenone	A ^e	<i>n</i> -Butyl benzoylacetate ^{c,j}	48	120-125	1		1.5180	21
<i>p</i> -Methylacetophenone	A ^h	<i>n</i> -Propyl <i>p</i> -methylbenzoylacetate ^{c,k}	66	130-135	2		1.5250	20
<i>p</i> -Chloroacetophenone	B ^a	Ethyl <i>p</i> -chlorobenzoylacetate ^l	70	123-125	2	37-40		
<i>p</i> -Methoxyacetophenone	A ^a	Ethyl <i>p</i> -methoxybenzoylacetate ^m	50	146-150	3		1.5422	20
<i>p</i> -Ethoxyacetophenone	B	Ethyl <i>p</i> -ethoxybenzoylacetate ⁿ	38			53-54		
Propiophenone	A ^a	Ethyl α -benzoylpropionate ^o	37	115-118	1		1.5080	25
		Ethyl 1-phenyl-1-propen-1-yl carbonate ^p	25	96-105	1		1.4960	25
Butyrophenone	A ^a	Ethyl α -benzoylbutyrate ^q	12	118-123	1.5		1.5075	21.5
		Ethyl 1-phenyl-1-buten-1-yl carbonate ^p	15	98-100	1.5		1.4885	21.5
Phenyl benzyl ketone	A	Ethyl benzoylphenylacetate	5			90-91		
Dibenzyl ketone	A	Ethyl α , γ -diphenylacetoacetate	45			77-79		
2-Acetonaphthone	A	Ethyl 2-naphthoylacetate	25			32-34		
Cyclohexanone	A	Ethyl 1-cyclohexen-1-yl carbonate ^{r,p}	20	92-94	12		1.438	24

^a Ethyl alcohol was distilled from reaction mixture at 150 mm. ^b 3-Ethyl-4-methyl-1-phenyl-5-pyrazolone, m. p. 111-112°. ^c New compound. ^d 3-*t*-Butyl-1-phenyl-5-pyrazolone, m. p. 110-111°. ^e 3-Isobutyl-1-phenyl-5-pyrazolone, m. p. 107-108°. ^f 3-*n*-Amyl-1-phenyl-5-pyrazolone, m. p. 95-96°; 3-*n*-amyl-1-*p*-nitrophenyl-5-pyrazolone, m. p. 113-115°. ^g 4-Ethyl-3-propyl-5-pyrazolone, m. p. 163-165°. ^h Potassium propylate was used and propyl alcohol was distilled from reaction mixture at 100 mm. pressure. ⁱ 3-*n*-Hexyl-1-phenyl-5-pyrazolone, m. p. 83-84°. ^j 1,3-Diphenyl-5-pyrazolone, m. p. 137-138°. ^k 3-*p*-Methylphenyl-5-isoxazolone, m. p. 131-133°. ^l 3-*p*-Chlorophenyl-1-phenyl-5-pyrazolone, m. p. 161. *Anal.* Calcd. for C₁₈H₁₁ClN₂O: Cl, 13.1. Found: Cl, 13.2. This compound has been reported by Wahl and Roland [*Chem. Zentr.*, 99, II, 1554 (1928)] but the melting point given was 140°. ^m 3-*p*-Methoxyphenyl-5-isoxazolone, m. p. 141-144°. ⁿ See experimental part. ^o 4-Methyl-3-phenyl-5-isoxazolone, m. p. 122-124°. ^p The product failed to react with phenylhydrazine or hydroxylamine, gave no coloration with alcoholic ferric chloride, and was hydrolyzed by alcoholic potassium hydroxide to potassium carbonate; it appeared to be identical with the enol carbonate prepared by Haller and Bauer.⁷ ^q 4-Ethyl-3-phenyl-5-isoxazolone, m. p. 88-90°. ^r Saponification equivalent, calcd. 85; found, 85.5. ^s Potassium butylate was used and butyl alcohol was distilled from reaction mixture at 18 mm. pressure.

to Dr. A. Q. Butler and Mr. Robert A. Burdett for the analyses reported.

Experimental

General Procedure.—The apparatus for condensing alkyl carbonates with ketones was similar to that previously described² for the carbalkoxylation of esters. It consisted of a 3-necked flask fitted with a piano wire stirrer, dropping funnel, and fractionating column.

The ketone was heated or digested with sodium or potassium alcoholate in a large excess of the alkyl carbonate. The yields were improved by maintaining the alcohol concentration as low as possible by fractionating from the mixture both the alcohol introduced with the metal alcoholate and the alcohol produced in the reaction. Equimolar proportions of ketone and metal alcoholate were employed, and the amount of alkyl carbonate corresponded to 4-8 moles per mole of ketone. To avoid mixed esters which might result from ester interchange, the alkyl carbonate and the metal alcoholate should be derived from the same alcohol. In Table I the alkyl carbonate employed in each case was derived from the same alcohol that occurs in the ester group of the product. Typical procedures are given below.

Ethyl β -Keto- δ , δ -dimethylcaproate (Example of method A).—Sodium (4.6 g.) was dissolved in anhydrous ethyl

alcohol (100 ml.) in a 500-ml., 3-necked flask arranged as described above. The solution was distilled to dryness and heated at reduced pressure until the sodium ethylate was substantially free of alcohol. After cooling, diethyl carbonate (125 ml.) was added and the cake of sodium ethylate was disintegrated. Methyl neopentyl ketone (23 g.) was added with stirring, and after ten minutes the bath was warmed to 50°. The sodium ethylate dissolved slowly. Alcohol was fractionally distilled out at a bath temperature of 110° and a pressure of 120 mm. during two and one-half hours. When no more alcohol was obtainable as distillate the mixture was cooled and acidified with acetic acid and agitated with water. The organic layer was washed free of acid with water and dried. Fractionation yielded 66% (24.5 g.) of ethyl β -keto- δ , δ -dimethylcaproate, boiling point 104-105° at 15 mm.; n_D^{20} 1.4333-5.

Anal. Calcd. for C₁₆H₁₈O₃: C, 64.4; H, 9.7. Found: C, 64.5; H, 10.1.

The product reacted with phenylhydrazine to give 3-neopentyl-1-phenyl-5-pyrazolone, m. p. 138-140°.

Anal. Calcd. for C₁₄H₁₅ON₂: N, 12.2. Found: N, 12.1.

Substitution of the carbethoxyl group on the methyl group of the original ketone was proved by condensation of the β -keto ester in the usual way with benzyl chloride

and hydrolysis of the product to hydrocinnamic acid which was identified by a mixture m. p. of its anilide.

Ethyl *p*-Ethoxybenzoylacetate (Example of method B).—Diethyl carbonate (500 ml.) and *p*-ethoxyacetophenone (82 g.) were placed in a 1-liter, 3-necked flask, arranged as described above. The reaction mixture was stirred, heated to refluxing, and a solution of sodium ethylate made from sodium (12 g.) and anhydrous ethyl alcohol (250 ml.) was added slowly from the dropping funnel, while alcohol was removed simultaneously as distillate at the head of the column. When no more alcohol was obtained as distillate the reaction mixture was cooled and poured onto a mixture of ice and hydrochloric acid. The organic layer was separated, washed free of acid, dried over calcium chloride and distilled until all diethyl carbonate had been removed. Since the residue tended to decompose when distillation was attempted at 2 mm. pressure, the product was purified by means of its copper salt. The residue was mixed with alcohol (100 ml.) and treated with a saturated, aqueous solution of copper acetate until no more precipitate formed. The green solid was filtered off and washed with alcohol. It was decomposed with a solution of acetic acid in the presence of ether and the ether layer was washed with water until free of copper. Evaporation of the ether yielded an oil which solidified and was recrystallized from a mixture of ether and petroleum ether; m. p. 50–53°, yield 38% (45 g.). After sublimation in a high vacuum at 87°, the m. p. was 53–54°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8. Found: C, 66.2; H, 6.8.

The keto ester was converted to 3-*p*-ethoxyphenyl-5-isoxazolone, m. p. 135–136°, by reaction with hydroxylamine.

Anal. Calcd. for $C_{11}H_{11}O_3N$: N, 6.8. Found: N, 6.8.

The keto ester was converted to 3-*p*-ethoxyphenyl-1-phenyl-5-pyrazolone, m. p. 152–153°, by reaction with phenylhydrazine.

Anal. Calcd. for $C_{17}H_{16}O_2N_2$: N, 10.0. Found: N, 10.0.

Ester of β -Keto- γ -methylvaleric Acid (Example of method C).—Methyl isopropyl ketone (50 g.) and diethyl carbonate (300 ml.) were stirred mechanically in a 500-ml. 3-necked flask and cooled to 2°. Alcohol-free sodium methylate (29 g.) was made into a thick paste with diethyl carbonate and added slowly to the reaction mixture. After two hours the reaction mixture was warmed and as much alcohol as possible fractionated out under a pressure of 200 mm. After cooling, the residue was acidified with acetic acid, agitated with water, and the organic layer was separated and fractionated. After removal of the excess diethyl carbonate an ester fraction was obtained boiling at 70–81° at 10 mm. and weighing 21.6 g. This was a mixture of methyl and ethyl esters of β -keto- γ -methylvaleric acid. An alcoholic solution of the product gave a red color when treated with a little ferric chloride, indicating the presence of an enolic group. The ester was converted to 3-isopropyl-1-phenyl-5-pyrazolone by reaction with phenylhydrazine. The product was sublimed in a high vacuum at 80° and then melted at 81–83°.

Anal. Calcd. for $C_{12}H_{14}ON_2$: C, 71.2; H, 7.0; N, 13.8. Found: C, 71.9; H, 7.0; N, 13.9.

Summary

A procedure is described for condensing alkyl carbonates with ketones by means of metal alcoholates to give β -keto esters. The new method has been applied to a variety of ketones.

ST. LOUIS, MISSOURI

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

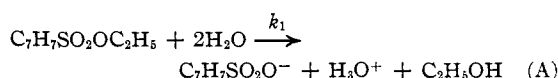
Rate and Mechanism in the Reactions of Ethyl *p*-Toluenesulfonate with Water, Hydroxyl Ions and Various Halide Ions¹

BY HAROLD R. McCLEARY AND LOUIS P. HAMMETT

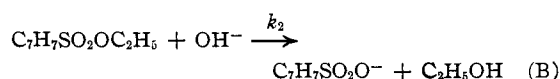
It is so generally true that, in a series of similarly constituted compounds, the rate of reaction parallels the thermodynamic stability that the exceptions are of special interest. This is all the more so because such exceptions must lie back of many important cases of homogeneous catalysis and many puzzling phenomena in the field of the Walden inversion.² The reactions of the alkyl halides offer a particularly striking example of this kind of exception, an example which is here ex-

tended by a quantitative study of the reactions of ethyl toluenesulfonate, which are closely related to the reactions of the alkyl halides.

The reactions investigated were the water reaction



and the displacements by hydroxyl ion (B) and halide ion (C)



(1) Dissertation submitted by Harold Russell McCleary in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(2) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 182.