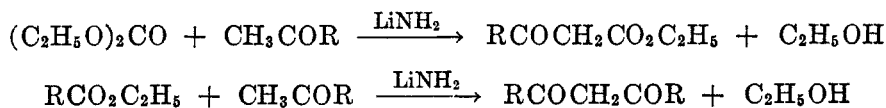


CONDENSATIONS EFFECTED BY THE ALKALI AMIDES. I. THE  
USE OF LITHIUM AMIDE IN THE SYNTHESIS OF CERTAIN  
 $\beta$ -KETO ESTERS AND SYMMETRICAL  $\beta$ -DIKETONES<sup>1</sup>

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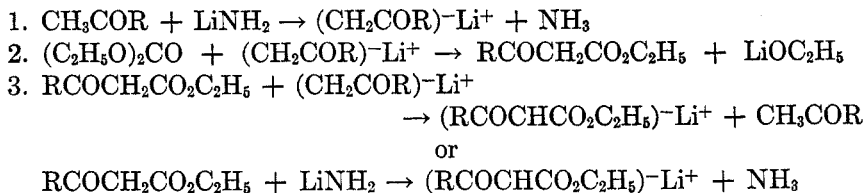
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The carbethoxylation of methyl ketones with diethyl carbonate to form  $\beta$ -keto esters has been effected previously by means of sodium ethoxide (1), sodium triphenylmethide (2), or sodium amide (3); and the acylation of ketones with ordinary esters has been effected by means of sodium metal (4), sodium ethoxide (5), sodium triphenylmethide (6), or sodium amide (6, 7). In the present investigation, these two types of condensations have been effected by lithium amide. The reactions may be illustrated by the following equations:



The method of carbethoxylation consists of adding the ketone to an ethereal suspension of lithium amide and refluxing the ethereal suspension of the lithium derivative of the ketone with diethyl carbonate. As was previously observed by Levine and Hauser (3), the presence of excess alkali amide increases the yield of  $\beta$ -keto ester appreciably. To see what effect the amount of lithium amide had on the yield of  $\beta$ -keto ester, the carbethoxylation of methyl isobutyl ketone was carried out with molecular equivalents of lithium amide and ketone and also with two equivalents of base to one of the ketone. The yield of  $\beta$ -keto ester using molecular equivalents of lithium amide and methyl isobutyl ketone was 39%. However, when two equivalents of base to one of ketone were used, the yield of product was 62%.

The following mechanism indicates how the presence of excess base might increase the yield of  $\beta$ -keto ester.



In the first step the ketone is converted completely to its lithium derivative by one equivalent of lithium amide. In the second step the lithioketone condenses with diethyl carbonate. One-half of the ketone could be regenerated in

<sup>1</sup> This work is based in part on a thesis to be submitted by Glenn R. Zellars in partial fulfillment of the requirements for the degree of Master of Science at the University of Pittsburgh.

the third step, thus making the maximum yield of the  $\beta$ -keto ester 50%. However, if two equivalents of lithium amide are used to one of the ketone, the third step of the reaction will be effected by the strongest base present (*i.e.*, the lithium amide) and the yield of the product may be theoretically 100%. In Table I are found the yields and boiling points of the  $\beta$ -keto esters which were prepared. It may be seen that these compounds have been prepared in fair

TABLE I  
 *$\beta$ -Keto Esters*

KETONE	$\beta$ -KETO ESTER	B.P.		YIELD, %	COPPER SALT M.P. (UNCOR.), °C
		°C	MM.		
Methyl <i>n</i> -propyl	Ethyl <i>n</i> -butyrylacetate	90-93	14	26	122-123 (8)
Methyl isobutyl	Ethyl isovalerylacetate	92-94	13	62	121.7-122 (9)
2-Acetylthiophene	Ethyl $\beta$ -keto- $\beta$ -(2-thi- enyl)propionate <sup>a</sup>	149-152	6	41	—
Acetophenone	Ethyl benzoylacetate	135-140	6	50	179-180 (10)

<sup>a</sup> 1-Phenyl-3-( $\alpha$ -thienyl)-pyrazolone-5, m.p. 135.2°. See ref. (3)

TABLE II  
 *$\beta$ -Diketones*

KETONE	ETHYL ESTER	PRODUCT	B.P.		YIELD, %	COPPER SALT M.P. (UNCOR.), °C
			°C	MM.		
Acetone	Acetate	Acetylacetone	139-141	757	50	decomp. (11)
Methyl ethyl	Propionate	Dipropionyl- methane <sup>a</sup>	78-81	30	51	209-210 (12)
Methyl <i>n</i> -propyl	<i>n</i> -Butyrate	Di- <i>n</i> -butyryl- methane	101-102	20	76	156-157 (14)
Methyl isobutyl	Isovalerate	Diisovaleryl- methane	114-116	20	75	157-158 (7)
Methyl <i>n</i> -amyl	Caproate	Dicaproylmethane	162-165	20	65	119-120 (7)
Acetophenone	Benzoate	Dibenzoylmethane <sup>b</sup>	77-78 (m.p.)		71	—

<sup>a</sup> The washings and filtrate from this copper salt were treated with 10% sulfuric acid and extracted with ether. After distilling off the solvent, there was obtained 11% of methyl propionylacetone, b.p. 93-99° at 30 mm; m.p. of copper salt 176-177.5°. See ref. (13).

<sup>b</sup> See ref. (15).

to good yields. These yields compare favorably with those obtained using sodium amide (3).

The method of acylation consists of adding the ketone to a stirred ethereal suspension of lithium amide and refluxing the ethereal suspension of the lithio-ketone with the appropriate ester. As observed above in the preparation of  $\beta$ -keto esters, the use of two equivalents of lithium amide to one of ketone increased the yields appreciably. In Table II are given the yields and boiling

points of the  $\beta$ -diketones prepared. In the acylation of methyl ethyl ketone with ethyl propionate, 11% of methyl propionylacetone (formed by acylation at the methylene carbon atom) was obtained in addition to the much higher yield of the methyl derivative. The production of both methyl and methylene derivatives in the acylation of ketones with esters has been observed earlier when sodium amide was used as the condensing base (6, 7).

#### EXPERIMENTAL<sup>2</sup>

*Preparation of lithium derivatives of ketones.* The apparatus used in these reactions consisted of a 500-cc. three-necked round-bottomed flask equipped with ground-glass joints, a mercury-sealed stirrer, a reflux condenser, and an addition funnel (protected from atmospheric moisture by a drying tube filled with Drierite). The reaction was carried out in a well-ventilated hood. Four-tenths of a mole (9.2 g.) of lithium amide was placed in the flask and covered with 100 cc. of absolute ether. The stirrer was started and 0.2 mole of the appropriate ketone, dissolved in 50 cc. of absolute ether, was added at such a rate as to keep the ether gently refluxing. If the refluxing became too violent, the reaction mixture was cooled with an ice-bath. After the addition of the ketone was complete (about 15 minutes), the reaction mixture was stirred for thirty minutes longer.

*Condensation of lithio-ketones with esters.* To the rapidly stirred suspension of the lithio-ketone, 0.4 mole of the required ester, dissolved in 50 cc. of absolute ether, was added. The reaction mixture was then stirred and refluxed for two hours on a water-bath.

*The isolation of  $\beta$ -keto esters.* The contents of the flask were poured onto a mixture of crushed ice and 125 cc. of concentrated hydrochloric acid. The two phases were separated and the aqueous phase was then extracted with several 100-cc. portions of ether. The ethereal phases were combined, dried over Drierite, and the ether distilled. The residue was first distilled at atmospheric pressure to remove the ketone and most of the excess diethyl carbonate and then *in vacuo* to obtain the  $\beta$ -keto ester. The yields of these compounds are given in Table I.

*The isolation of  $\beta$ -diketones.* The reaction mixtures were decomposed as described above for the  $\beta$ -keto esters. After distilling off the ether, the residue was dissolved in an equal volume of methanol and then poured into 350 cc. of a hot saturated solution of copper acetate. The copper salts of the  $\beta$ -diketones usually separated out as blue solids. The flask containing the copper salt was placed in a refrigerator over night to allow the precipitation of the salt to become complete. The copper salts were then filtered and washed with ice-cold low-boiling petroleum ether until the washings were practically colorless. The crude copper salt was poured into a separatory funnel and shaken with 10% sulfuric acid and ether until decomposition of the copper chelate was complete and two homogeneous phases were present. The phases were separated and the ethereal solution was dried over Drierite. The ether was distilled off at atmospheric pressure and the residue distilled *in vacuo*. The yields of the  $\beta$ -diketones are given in Table II.

#### SUMMARY

Various ketones have been carbethoxylated with diethyl carbonate in the presence of lithium amide to give  $\beta$ -keto esters in fair to good yields.

Certain ketones have been acylated with aliphatic and aromatic esters to produce symmetrical  $\beta$ -diketones in good yields.

As previously observed with sodium amide (7), the acylation of methyl ethyl

<sup>2</sup> The lithium amide used in this investigation was purchased from the A. D. Mackay Company of New York.

ketone with ethyl propionate in the presence of lithium amide produces both methyl and methylene derivatives.

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