[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Carbethoxylation and Carbonation of Ketones Using Sodium Amide. Synthesis of β-Keto Esters[1]

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The carbalkoxylation of ketones with alkyl carbonates and the carbonation of ketones, followed by esterification of the resulting β-keto acids, are useful ways of preparing β-keto esters. The general reactions may be represented by the following scheme, but they are not limited to methyl ketones.

$$\begin{tikzcd}
\mathrm{RCOCH_3} \arrow[rr, "(R'O)_2CO"] \arrow[dr, "CO_2"'] & & \mathrm{RCOCH_2CO_2R'} \\
& \mathrm{RCOCH_2COOH} \arrow[ur, "\text{esterification}"'] &
\end{tikzcd}$$

In 1941 Wallingford, Homeyer and Jones[2] reviewed earlier carbalkoxylations and described a general method for effecting the reaction using sodium or potassium alkoxides under forced conditions. Although their method is satisfactory with a number of ketones, it fails with relatively reactive ketones, such as methyl ethyl ketone and benzalacetone, and with relatively unreactive ketones, such as di-isobutyl ketone and camphor. Moreover, certain ketones, for example, cyclohexanone, give the carbethoxyl derivative of the enol form of the ketone. Recently, in this Laboratory, certain of these ketones were converted to β-keto esters by carbethoxylation with diethyl carbonate or by carbonation (followed by esterification) using sodium[3] or potassium triphenylmethide.[4] The present paper describes general methods for effecting these types of reactions using sodium amide. This base has previously been used for this purpose in relatively few cases.[5]

Our method of carbethoxylation consists in converting the ketone into its sodium derivative by means of sodium amide in liquid ammonia, replacing the liquid ammonia by absolute ether and refluxing the ether suspension of the sodio ketone with diethyl carbonate. Similar to the acylation of ketones with esters to form β-diketones reported recently,[6] the presence of excess sodium amide has a favorable effect on the yields of β-keto esters in the carbethoxylation of ketones. Thus with methyl isobutyl ketone, the yield (based on the ketone) of β-keto ester was 41% using molecular equivalents of sodium amide and ketone, but 64% using two equivalents of sodium amide to one of the ketone. The higher yield in the presence of excess sodium amide is understandable on the basis of the mechanism of the reaction, which may be represented with methyl ketones by the following three steps.

(1) $CH_3COR + NaNH_2 \longrightarrow (CH_2COR)^-Na^+ + NH_3$

(2) $C_2H_5OCO_2C_2H_5 + (CH_2COR)^-Na^+ \longrightarrow RCOCH_2CO_2C_2H_5 + NaOC_2H_5$

(3) $RCOCH_2CO_2C_2H_5 + (CH_2COR)^-Na^+ \longrightarrow (RCOCHCO_2C_2H_5)^-Na^+ + CH_3COR$

or

$RCOCH_2CO_2C_2H_5 + NaNH_2 \longrightarrow (RCOCHCO_2C_2H_5)^-Na^+ + NH_3$

Although the ketone is converted completely into its sodium derivative by an equivalent of sodium amide in the first step, one-half of it could theoretically be regenerated in the third step. An extra equivalent of sodium amide, however, keeps the ketone in the form of its sodium derivative and makes possible the carbethoxylation of all of the ketone. Of course it is also possible for the extra equivalent of sodium amide to react with the diethyl carbonate, but apparently this occurs to no great extent. In Table I are given the results obtained using two equivalents each of sodium amide and diethyl carbonate to one of the ketone. Similar to acylations in the presence of sodium amide, the carbethoxylation of methyl ethyl ketone forms, in addition to the expected methyl derivative, ethyl propionylacetate, some of the methylene derivative, ethyl α-methylacetoacetate. It is possible that small amounts of the methylene derivatives were formed also with the higher methyl-methylene ketones, but none was found.

Our method of carbonation consists in transferring an ether suspension of the sodium derivative of the ketone, prepared as in carbethoxylations, onto dry ice. The mechanism of the reaction with methyl ketones may be represented by the two steps.

(1) $RCOCH_3 + NaNH_2 \longrightarrow (RCOCH_2)^-Na^+ + NH_3$

(2) $CO_2 + (RCOCH_2)^-Na^+ \longrightarrow RCOCH_2COO^-Na^+$

Although an equivalent of sodium amide may produce maximum yields in the carbonation, an excess of the base has generally been employed in order to minimize possible self-condensation of the ketone. The resulting β-keto acids have been esterified with diazomethane to form methyl β-keto esters, the yields of which are given in Table II. In contrast to the carbethoxylation of methyl ethyl ketone, the carbonation of this ketone appeared to form only the methyl derivative, propionylacetic acid; however, a small amount of the

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[1] Paper XXVIII on "Condensations"; paper XXVII, THIS JOURNAL, **66**, 1231 (1944).

[2] Wallingford, Homeyer and Jones, *ibid.*, **63**, 2252 (1941).

[3] Baumgarten, Levine and Hauser, *ibid.*, **66**, 862 (1944).

[4] Levine, Baumgarten and Hauser, *ibid.*, **66**, 1230 (1944).

[5] Apparently only acetone has been carbethoxylated using sodium amide (Lux, *Ber.*, **62B**, 1827 (1929), while only camphor and a few cyclic ketones have been carbonated by means of this base (Bredt, *J. prakt. Chem.*, [2] **104**, 9 (1922); [2] **131**, 132 (1932); Gardner, Perkin and Watson, *J. Chem. Soc.*, **97**, 1756 (1910); Koetz and Grethe, *J. prakt. Chem.*, [2] **80**, 473 (1909)).

[6] Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944).

TABLE I

β-KETO ESTERS FROM KETONES BY CARBETHOXYLATION[a]

Ketone	β-Keto ester	B. p. °C.	Mm.	Yield, %
Methyl ethyl	Ethyl propionylacetate[b]	91–93	17	13[d]
	Ethyl α-methylacetoacetate[c]	82.5–84	15	9[d]
Methyl *n*-propyl	Ethyl *n*-butyrylacetate[e]	93–95.5	15	19
Methyl isobutyl	Ethyl isovalerylacetate[f]	96.5–99.5	14	64
Methyl *n*-hexyl	Ethyl *n*-heptanoylacetate[g]	122.5–126	10	52
Methyl *t*-butyl	Ethyl γ,γ,γ-trimethylacetylacetate[h]	96–98	15	40
Di-isobutyl	Ethyl isovalerylisovalerate[i]	118–119.5	15	20
Acetophenone	Ethyl benzoylacetate[j]	149–151	12	64
Cyclohexanone	2-Carbethoxycyclohexanone[k]	106–109	11	18
Camphor	Ethyl ester of camphor carboxylic acid[l]	159–161	19	20
2-Acetothienone	Ethyl β-keto-β-(2-thienyl)-propionate[m]	150–153	5	48

TABLE II

β-KETO ESTERS FROM KETONES BY CARBONATION FOLLOWED BY ESTERIFICATION WITH DIAZOMETHANE

Ketone	β-Keto ester	B. p. °C.	Mm.	Yield, %
Methyl ethyl	Methyl propionylacetate[n]	73–76	15	25
Methyl *n*-propyl	Methyl *n*-butyrylacetate[o]	82.5–85	15	30
Methyl isobutyl	Methyl isovalerylacetate[p]	93–96	20	61
Methyl *n*-hexyl	Methyl *n*-heptanoylacetate[g]	109–113	8	48
Methyl *t*-butyl	Methyl γ,γ,γ-trimethylacetylacetate[h]	82–84	17	41
Di-isopropyl	Methyl isobutyrylisobutyrate[q]	93	27	60
Di-isobutyl	Methyl isovalerylisovalerate[i]	114–115	15	38
Acetophenone	Methyl benzoylacetate[r]	151–152	15	50
Butyrophenone	Methyl benzoyl-*n*-butyrate[s]	154–155	13	61
Cyclohexanone	2-Carbomethoxycyclohexanone[k]	94–95	10	38
Camphor	Methyl ester of camphor carboxylic acid[l]	142–143	12	70

NOTES FOR TABLES I AND II

[a] Microanalyses by Dr. T. S. Ma, University of Chicago, Chicago, Illinois. [b] Copper salt, m. p. 144–145°, Dupont, *Compt. rend.*, **148**, 1524 (1909). [c] 1-Phenyl-3,4-dimethylpyrazolone-5, m. p. 118–119.5°, Knorr, *Ann.*, **238**, 162 (1887). [d] When the sodium derivative of methyl ethyl ketone was prepared by adding the ketone to an ether suspension of sodium amide followed after five minutes by diethyl carbonate, the yield of ethyl propionylacetate was 14% and that of ethyl α-methylacetoacetate was 8%. [e] Copper salt, m. p. 124–126°, Mouréu and Delange, *Bull. soc. chim.*, [3] **29**, 667 (1903). [f] Copper salt, m. p. 122°, Wahl and Doll, *ibid.*, [4] **13**, 273 (1913). [g] 3-*n*-Hexyl-1-phenylpyrazolone-5, m. p. 83–84°, see ref. 2. [h] 3-*t*-Butyl-1-phenylpyrazolone-5, m. p. 110.5–111°, see ref. 3. [i] Acidic cleavage gave isovaleric acid, identified by its anilide, m. p. 109–110°, see ref. 3. [j] Copper salt, m. p. 179–180°, Feist, *Ber.*, **23**, 3737 (1890). [k] 1-Phenyl-3,4-cyclotetramethylenepyrazolone-5, m. p. 177°. *Anal.* Calcd. for $C_{13}H_{14}ON_2$: C, 72.89; H, 6.53; N, 13.08. Found: C, 72.93; H, 6.51; N, 13.10. This compound has been reported by Dieckman [*Ann.*, **317**, 94 (1901)] but the melting point was given as 165°. [l] The phenylpyrazolone of camphor-carboxylic acid, m. p. 157–158°. *Anal.* Calcd. for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.10; H, 7.55; N, 10.39. This compound has been reported by Bruhl [*Ber.*, **24**, 3394 (1891)] but the melting point was given as 132°. [m] 1-Phenyl-3-(α-thienyl)-pyrazolone-5, m. p. 137° cor. *Anal.* Calcd. for $C_{13}H_{10}ON_2S$: N, 11.56. Found: N, 11.10. [n] Copper salt, m. p. 160°, see ref. 3. Because of the solubility of propionylacetic acid, a minimum of water (50 cc.) is added to the reaction mixture after carbonation. [o] Copper salt, m. p. 133–134.5°, Bouveault and Bongert, *Bull. soc. chim.*, [3] **27**, 1090 (1902). [p] Copper salt, m. p. 141–143°, *ibid.*, p. 1092. [q] Acidic cleavage gave isobutyric acid, identified by its anilide, m. p. 104.5–106°, see ref. 3. [r] Copper salt, m. p. 200–201°, Wahl, *Compt. rend.*, **147**, 74 (1908). [s] 4-Ethyl-3-phenylisoxazolone-5, m. p. 88–90°, see ref. 2.

methylene derivative might have escaped detection.

Examples of ketones that may be carbethoxylated satisfactorily using either sodium ethoxide or sodium amide are methyl isobutyl and methyl *n*-hexyl ketones and acetophenone. Even though twice as much sodium amide as sodium ethoxide is employed to convert the same amount of ketone to β-keto ester, we prefer to use sodium amide, since the carbethoxylation can be effected in considerably less time with this base. Methyl *t*-butyl ketone, which gives only a poor yield in the presence of sodium ethoxide, gives a 40% yield using sodium amide. Methyl ethyl and di-isobutyl ketones, cyclohexanone and camphor, which fail to yield β-keto esters in the presence of sodium alkoxides, can be carbethoxylated using sodium amide but the yields are only fair (Table I). Better yields of β-keto esters have been obtained from these ketones by carbonation followed by esterification (Table II). The latter method is also satisfactory with diisopropyl ketone and butyrophenone, neither of which has yet been carbethoxylated satisfactorily. On carbonation, benzalacetone appears to form some (17% by titration of the ether extract) of the corresponding β-keto acid, but the β-keto ester has not yet been obtained in the pure condition.

Although sodium or potassium triphenylmethide is satisfactory for the carbethoxylation or carbonation of certain ketones, sodium amide is generally to be preferred, since this base is more available. Only in one case, that of the carbonation of methyl ethyl ktone, has the yield been appreciably better using sodium[3] or potassium[4] triphenylmethide instead of sodium amide.

Experimental

Carbethoxylations.—In a 500-cc. three-necked round-bottomed flask (having ground glass joints) equipped with a mercury-sealed stirrer, a separatory funnel and a dry-ice reflux condenser[7] (having a soda lime tube), was placed 300 cc. of commercial anhydrous liquid ammonia. To the stirred solution was added the minimum of sodium to produce a blue color. A few crystals of ferric nitrate were added followed by 0.6 mole of clean pieces of sodium. When the sodium had been converted to sodium amide (assumed to be quantitative), 0.3 mole of the ketone in 100 cc. of absolute ether was added over a period of five minutes. The dry-ice condenser was replaced by a water reflux condenser and the reaction flask, containing the sodium derivative[8] of the ketone, was placed on a steam-bath. The ammonia was evaporated as rapidly as possible (during fifteen to twenty minutes), sufficient ether being added to maintain the volume at approximately 300 cc. When the ether began to reflux, indicating that all the liquid ammonia had evaporated, 0.6 mole of diethyl carbonate was added and the mixture stirred and refluxed for two hours. The reaction mixture was stirred into 45 cc. of glacial acetic acid and approximately 500 g. of crushed ice, and the reaction flask rinsed with ether. The ether phase was washed with saturated sodium bicarbonate solution, dried with Drierite, and the solvent distilled. The excess diethyl carbonate was distilled at atmospheric pressure and the residue fractionated *in vacuo*. The yields and boiling points of the β-keto esters are given in Table I.

Carbonation Followed by Esterification.—The sodium derivative of the ketone was prepared in liquid ammonia from 0.625 mole of sodium amide and 0.5 mole of ketone, and the ammonia replaced as rapidly as possible by absolute ether as described above in carbethoxylations. As soon as the ether began to reflux, the mixture containing the suspension of the sodium derivative of the ketone was poured onto a ten-fold excess .of dry-ice and the flask rinsed with absolute ether. After the reaction mixture had come to room temperature, ether and a minimum of water were added until two homogeneous layers were present. The aqueous phase was cooled to 0°, acidified with iced sulfuric acid (30 cc. of acid and 200 g. of crushed ice) and the liberated β-keto acid extracted with ether until titration showed the extraction to be complete. After drying with sodium sulfate at 0° for one-half hour, the ether solution was treated with a 10–20% excess of diazomethane (prepared from nitrosomethyl urea)[9] and the excess diazomethane destroyed by adding glacial acetic acid until the reaction mixture was acid to litmus or the yellow color characteristic of the diazomethane disappeared. The ether phase was washed with saturated sodium bicarbonate, dried over Drierite, the solvent distilled, and the residue fractionated *in vacuo*. The yields and the boiling points of the β-keto esters are given in Table II. In general the yields of the β-keto esters were within 10% of those of the corresponding β-keto acids determined by titration of the ether extracts.

Identification of β-Keto Esters.—In most cases the β-keto esters were identified by their copper salts or their phenylpyrazolones (see notes to Tables I and II). The β-keto esters obtained from di-isopropyl and di-isobutyl ketones, which fail to exhibit these active hydrogen or carbonyl group reactions, were subjected to acidic cleavage by means of sodium ethoxide in absolute alcohol as described previously,[3] and the resulting isobutyric or isovaleric acid identified. In addition to the acid, there was isolated a small amount of the corresponding ketone (3–4% of di-isobutyl ketone isolated as its 2,4-dinitrophenylhydrazone), which might have resulted in three ways: (a) by reverse carbethoxylation, (b) ketonic cleavage brought about by traces of sodium hydroxide present, or (c) by cleavage of the carbethoxyl derivative of the enol form of the ketone. We believe that the β-keto esters were not contaminated with an appreciable amount of the carbethoxyl derivative of the enol form of the ketone since their boiling points were essentially constant. Also, under similar conditions authentic ethyl α-isopropylacetoacetate (prepared by the alkylation of ethyl acetoacetate)[10] gave a small amount (1–2%) of its corresponding ketone, methyl isobutyl ketone, while ethyl isovalerylacetate, prepared by the carbethoxylation of methyl isobutyl ketone, regenerated a similar small amount (1–2%) of the ketone.

Summary

1. General methods are described for converting ketones to β-keto esters by carbethoxylation with diethyl carbonate and by carbonation (followed by esterification) using sodium amide.

2. These methods are satisfactory with several ketones that fail to be carbalkoxylated in the presence of sodium or potassium alkoxides.

3. The presence of excess sodium amide has a favorable effect on the yields of β-keto esters on carbethoxylation. This is accounted for on the basis of the mechanism.

4. On carbethoxylation, in the presence of sodium amide, methyl ethyl ketone forms both the methyl and the methylene derivatives.

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(7) An ordinary condenser may be used, but if this is done an extra 100 cc. of ammonia should be present.

(8) Methyl isobutyl ketone is evidently converted quickly and completely to its sodium derivative by sodium amide in liquid ammonia. This is shown by the fact that when the ketone is added to sodium amide in liquid ammonia, containing a small amount of sodium triphenylmethide (obtained by adding triphenylmethane), the deep red color of the triphenylmethide ion is destroyed practically as soon as an equivalent of ketone is added.

(9) Arndt, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1943, 2nd Coll. Vol., p. 166 (Note 3), p. 461.

(10) Hauser and Breslow, THIS JOURNAL, **62**, 2389 (1940).