Studies on Pyrethrins
The Synthesis of Some β-Keto Esters

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Several methods are reported to prepare β-keto-esters through the condensation of methyl ketones and ethyl carbonate. The typical methods are those which use, as condensation agent, sodium alcoholate,⑴ sodamide⑵ and more recently sodium hydride.⑶ Though the reaction yields depend upon the character of methyl ketones which are used, the best results can generally be obtained by employing sodium hydride, and the next best by sodium alcoholate. The sodamide method yields usually poor results, but is exempted from inconveniences which accompany the former two methods such as the work in the stream of nitrogen gas or the stirring under reduced pressure and the use of large excess of diethyl carbonate.

We, therefore, investigated the method to increase the condensation yield in the reaction by sodamide. We performed the reaction and found that the low yield of the reaction is due to the formation of urethan by a side reaction of this condensation.

A mechanism of this condensation proposed by Levine⑵ is as follows;

$$\text{(I)}\quad CH_3COR+NaNH_2 \longrightarrow (CH_2COR)^-Na^+ + NH_3$$

$$\text{(II)}\quad C_2H_5OCO_2C_2H_5+(CH_2COR)^-Na^+ \longrightarrow RCOCH_2COOC_2H_5+NaOC_2H_5$$

$$\text{(III)}\quad RCOCH_2CO_2C_2H_5+(CH_2COR)^-Na^+ \longrightarrow (RCOCHCOOC_2H_5)^-Na^+ + CH_3COR$$

$$\text{or}\quad RCOCH_2CO_2C_2H_5+NaNH_2 \longrightarrow (RCOCHCOOC_2H_5)^-Na^+ + NH_3$$

The equations are correct as far as the mechanism is concerned, but the following side reactions also occur in reality. A part of ammonia produced in (I) and (III) reacts with diethyl carbonate and yields urethan and alcohol when two molecules of sodamide are used for one molecule of methyl ketones

$$\text{(IV)}\quad C_2H_5OCO_2C_2H_5+NH_3 \longrightarrow NH_2CO_2C_2H_5+C_2H_5OH$$

and the alcohol which is produced reacts with sodium enolate of the methyl ketone or with sodamide to produce ammonia.

$$\text{(V)}\quad C_2H_5OH+(CH_2COR)^-Na^+ \longrightarrow CH_3COR+C_2H_5ONa$$

$$\text{or}\quad C_2H_5OH+NaNH_2 \longrightarrow C_2H_5ONa+NH_3$$

The methyl ketone liberated by this reaction reacts sodamide and liberates ammonia, and ammonia repeats the reactions already described though ammonia decreases gradually by escaping from the reaction system. Thus we found that in order to minimize the reaction between ammonia and diethyl carbonate, it is necessary to produce sodium enolate of the methyl ketone at first, and in order to complete enolization of the methyl ketone or to complete the production of keto ester as far as possible, it is also necessary to employ more than two molecules of sodamide and more than one molecule, or probably more than two molecules, of diethyl carbonate to one molecule of the methyl ketone.

By using a methyl ketone, sodamide and diethyl carbonate in the molar ratio of 1:3:3 in the procedure described in the experimental part, we succeeded in obtaining almost the same yields of β-keto ester (See Table 1) as in the case of sodium hydride when the methyl

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(1) Wallingford et al., *J. Am. Chem. Soc.*, **63**, 2252 (1941).

(2) R. Levine and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1768 (1944).

(3) S. B. Soloway and F. B. LaForge, *J. Am. Chem. Soc.*, **69**, 2677 (1947).

Table 1

ketones	products	b. p.	n_D (temp., °C.)	yield %				Analytical Data %	
				$NaOCH_3$ method	old $NaNH_2$ method	NaH method	the present method	Found	Calcd.
Methyl ethyl ketone	Ethyl 3-oxo-valerate	91—93°/ 17 mm	1.4183 (23°)		13(2)		11	C 57.62 H 7.83	C 58.33 H 8.33
Methyl n-propyl ketone	Ethyl-3-oxo-caproate	93-95.5°/ 15 mm	1.4240 (30°)		19(2)		48	OC_2H_5 28.6	OC_2H_5 28.2
Allyl-acetone	Ethyl 3-oxo-6-heptenoate	95-100°/ 11 mm	1.4414 (22°)	70(4)		77(4)	70	OC_2H_5 25.8	OC_2H_5 26.5
Methallyl-acetone	Ethyl 3-oxo-6-methyl-6-heptenoate	105-115°/ 12.5 mm	1.4493 (15°)			70(4)	70	C 64.87 H 8.65	C 65.21 H 8.70
5-Hepten-2-one	Ethyl 3-oxo-6-octenoate	90-104°/ 7 mm	1.4397 (30°)			85(8)	69.5	OC_2H_5 25.0	OC_2H_5 24.4
6-Hepten-2-one	Ethyl 3-oxo-7-octenoate	102-120°/ 9.5 mm	1.4384 (30°)				75.5	OC_2H_5 24.9	OC_2H_5 24.4
Piperonyl-acetone	Ethyl 3-oxo-5-(3,4-methylene-dioxy-phenyl)-valerate	160-163°/ 3 mm	1.5111 (30°)				32	C 63.32 H 6.10	C 63.63 H 6.07
Furfuryl-acetone	Ethyl 3-oxo-5-furylvalerate	110-120°/ 3 mm	1.4758 (16°)				22	C 64.78 H 7.05	C 62.86 H 6.67
Benzyl-acetone	Ethyl 3-oxo-5-phenyl-valerate	129-138°/ 7 mm	1.4972 (17°)				40.9	C 71.43 H 7.34	C 70.91 H 7.21
Tetrahydro-furfuryl-acetone	Ethyl 3-oxo-5-(2-tetrahydro-furfuryl) valerate	110-117°/ 3 mm	1.4448 (31°)				38	OC_2H_5 23.62	OC_2H_5 21.08

ketone is stable to alkali.

This research is a part of the synthetic study of pyrethrin and cinerin homologues and several 3-methyl-2-cyclopenten-4-ol-1-ones (See Table 2)—some of them are not yet known—have been synthesized by the condensation of methyl glyoxal with these keto esters through the methodes of LaForge et al.(4) or Matsui et al.(5)

Experimental

A. Methyl Ketones

(1) **6-Hepten-2-one.**—Buten-(1)-ol-(4) (b. p. 112-114°) was prepared in 30% yield from allyl bromide and paraformaldehyde, and 4-bromobutene-(1) (b. p. 94-100°) in 64% yield from this butenol by the method of Linstead and Rydon.(6) A solution of sodium methylate prepared by dissolving 12 g. (ca. 0.5 mol.) of sodium in 200 cc. of absolute methanol was cooled to 15° and 70 g. (0.54 mol.) of ethyl acetoacetate was added to the stirred solution. After 1.5 hrs. 68 g. (0.5 mol.) of the above 4-bromobutene was added at once and the reaction was completed by refluxing for five hours. Most of the methanol was removed by distillation and water was added to the residue. Crude ethyl α-3-butenylacetoacetate separated as an upper layer and weighed 57.7 g..

One hundred and thirty eight grams of this crude keto ester and 70 g. of potassium hydroxide in 1.3 l. of water were stirred at 20° for 7 hrs.. The oil was extracted with petroleum ether and discarded. A mixture of 50 cc. of concentrated sulfuric acid and 80 cc. of water was added to the aqueous solution and the mixture was warmed under stirring on a water bath until the evolution of carbone dioxide ceased. The upper oily layer was separated, and the aqueous layer was saturated with sodium chloride and was extracted with petroleum ether. The oil and the petroleum extracts were combined and washed with dilute alkali and saturated sodium chloride solution and dried with potassium carbonate. After evaporation of the solvent, the residue was distilled. 6-Hepten-2-one distilled at 145-150°, yield 42 g. (50 % of the theory based on the crude ester)

(2) **Piperonylacetone.** — One hundred fifty grams of piperonylideneacetone was dissolved in

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(4) M. S. Schechter, N. Green and F. B. LaForge, *J. Am. Chem. Soc.*, **71**, 3165 (1949).

(5) M. Matsui, T. Kato et al, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **71**, 235 (1950).

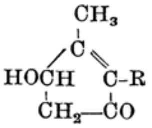
(6) *J. Chem. Soc.*, **1934**, 1996

(7) Kaufmann and Radosevic, *Ber.*, **49**, 679 (1916).

(8) F. B. LaForge et al., *J. Am. Chem. Soc.*, **70**, 3708 (1948).

Table 2

2-Substituted 3-methyl-2-cyclopenten-4-ol-1-ones

	b. p.	n_D	yield %*	Analytical Data
Methyl	108–110°/ 0.29 mm.	1.5079/ 26°	31	Found: C, 68.01; H, 7.85. Calcd. for $C_7H_{10}O_2$: C, 66.67; H, 7.92%.
Ethyl	132–135°/ 1.3 mm.	1.5082/ 28.5°	30.8	Found: C, 68.40; H, 8.37. Calcd. for $C_8H_{12}O_2$: C, 68.57; H, 8.57%.
Allyl	132–135°/ 1 mm.	1.5141/ 25°	34	Semicarbazone, m. p. 210° Found: C, 56.73; H, 7.20. Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.23%.
Methallyl	121–126°/ 0.2 mm.	1.5120/ 12°	24	Semicarbazone, m. p. 208–209° Found: C, 59.10; H, 7.25; N, 19.01. Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.19; H, 7.68; N, 18.83%.
2-Butenyl (trans-cinerolone)	127–132°/ 0.5 mm.	1.5096/ 18.5°	45	Semicarbazone, m. p. 208–209° Found: C, 59.79; H, 7.53: N, 19.28. Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.19; H, 7.68; N, 18.83%.
3-Butenyl	126–132°/ 0.5 mm.	1.5151/ 18°	41	Semicarbazone, m. p. 187° Found: C, 59.73; H, 7.40; N, 19.09. Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.19; H, 7.68; N, 18.83%.
Benzyl	161–165°/ 0.15 mm.	1.5680/ 21°	20	Semicarbazone, m. p. 215–216°. Found; C, 64.79; H, 6.48; N, 16.41. Calcd. for $C_{14}H_{17}O_2N_3$: C, 64.87; H,6.56; N, 16.23%.
Piperonyl	146–150°/ 0.23 mm.	1.5670/ 23°	21	Found: C, 68.84; H, 5.21. Calcd. for $C_{14}H_{14}O_4$: C, 68.29;H, 5.59%.
Furfuryl	140–143°/ 0.6 mm.	1.5352/ 16°	38	Semicarbazone, m. p. 201–202° (from ethanol). Found: C, 56.98; H, 6.79; N, 16.97. Calcd. for $C_{12}H_{15}O_3N_3$: C, 57.83; H, 6.02; N,1 6.86%. 3, 5-Dinitrobenzoate, m. p. 168–169° Found: C, 55.71; H, 4.28; N, 7.18 Calcd. for $C_{18}H_{14}O_8N_2$: C, 55.95; H, 3.65; N, 7.25%. p-Nitrobenzoate, m. p. 108–109° Found: C, 63.38; H, 4.94; N, 4.10. Calcd. for $C_{18}H_{15}O_6N$: C, 63.34; H, 4.43; N, 4.16%.
Tetrahydrofurfuryl	113–120°/ 0.1 mm.	1.5095/ 19°	4	Found: C, 68.15; H, 7.06. Calcd. for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16%.

* The yields are based on the ester used.

300 cc. of ethyl acetate and reduced with an equivalent amount of hydrogen at 10 atm. in the presence of 10 g. of Raney nickel at room temperature to piperonylacetone, b. p. 152-158°/5 mm. (the reported b. p. 164-5°/12 mm.⑺), yield 105 g. (71% of theory).

(3) Tetrahydrofurfurylacetone.

(i) Tetrahydrofurfurylpropanol-(2). Two hundred and eighty grams of furfurylidene acetone was hydrogenated with 4 equivalent molecules of hydrogen at 40 atm. in the presence of 25 g. of Raney nickel together with some water at 90-120°. The product, boiling 122-131°/24 mm., n_D^{22} 1.4519, was collected, yield 175 g. (62% of theory) (Found: C, 66.14; H, 10.88. Calcd. for $C_8H_{16}O_2$: C, 66.66; H, 11.11%.)

(ii) Tetrahydrofurfurylacetone. Seventy-two grams of tetrahydrofurfuryl-propanol was oxidized with a mixture of 49 g. of potassium bichromate, 70 g. of concentrated sulfuric acid and 250 cc. of water at 60°. The product was extracted with ether. After distillation 31 g. of tetrahydrofurfurylacetone, boiling at 112-115°/28 mm., n_D^{27} 1.4414, was obtained; 2.4-Dinitrophenylhydrazone, yellow crystal, m. p. 76.5°-78.5°C. (Found: N, 17.51. Calcd. for $C_{14}H_{18}O_5N_4$: N, 17.34%).

B. β-Keto-Esters

The general procedure is as follows: one mol. of a methyl ketone is added at a time under stirring to about 3 mols. of sodamide in 1 l. of dry ether at 0° in an ice bath; after 15 minutes the bath is removed and stirring is continued another one hour and then refluxed 15 minutes in a water bath. The bath is replaced by the ice bath and about three mols. of diethyl carbonate is dropped as rapidly as possible. Stirring and refluxing is continued for 4 hours. After cooling three mols. of glacial acetic acid is added and then 600 cc. of water. The upper ether layer is separated and the ether is recovered by distillation. The residual oil is dissolved in an equal volume of petroleum ether and washed several times with an equal volume of water in order to remove a small quantity of urethan. The urethan can be recovered by extracting the water solution with ether. The petroleum ether solution is dried on anhydrous sodium sulphate or magnesium sulphate. After evaporation of the petroleum ether, the β-keto ester is distilled under reduced pressure.

Summary

A new procedure for preparing β-keto esters from methyl ketones, sodamide and diethyl carbonate using these reagents in the molar ratio of 1:3:3 is reported. The yields of β-keto esters approach to those of the preparation using sodium hydride as condensing agent. Furthermore, some cyclopentenolones were prepared from the β-keto esters synthesized by this procedure.

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