[CONTRIBUTION FROM THE LABORATORIES OF W. J. BUSH & CO., LTD.]

Synthesis of α-Bromoketones

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A new synthesis of α-bromoaldehydes based upon the bromination of enol acetates of aldehydes was described in a previous paper.[2] The simplicity of this method and the higher yields obtained as compared with previously reported syntheses indicated the desirability of its application to the synthesis of α-bromoketones.

It was apparent from a survey of the literature that ketones do not yield enol acetates as readily as do aldehydes. Hancu[3] prepared the enol acetate of diethyl ketone and dipropyl ketone by heating them with acetic anhydride and sodium acetate. The same procedure failed to give any enol acetates with aliphatic methyl ketones. The enol acetates of cyclic ketones such as cyclohexanone and homologs were obtained with greater ease[4] especially when phosphoric acid was used as a catalyst.[5] Gwynn and Degering[6] obtained a number of enol acetates by the interaction of ketene with ketones in the presence of sulfuric acid as a catalyst. There appears to be one other synthesis of enol acetates (alkyl vinyl acetates) of ketones[7] based upon the addition of organic acids to alkyl acetylenes.

The applicability of the method under discussion in this paper to the synthesis of α-bromoketones seemed to depend upon a simple preparation of ketone enol acetates. A search was made for a suitable catalyst which would give the enol acetate directly from the ketone. Potassium acetate, phosphoric acid and sulfuric acid were tried in various concentrations without success. Finally, *p*-toluenesulfonic acid was found to be suitable for this reaction. In all these experiments, methyl *n*-amyl ketone, propiophenone and cyclohexanone were taken as being representative of a wide range of ketones.

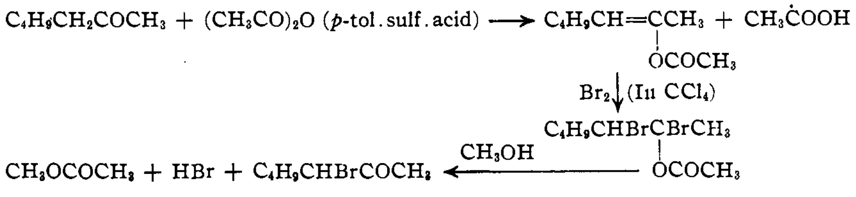
Bromination of aliphatic methyl ketones involves the possibility of substitution of either the methylenic or methyl hydrogen atom. It is of interest to note that it is the methylenic hydrogen which is first replaced in all cases.[8] It is also significant that in the present investigation methyl *n*-amyl ketone gave an enol acetate exclusively from the methylenic hydrogen. This was proved by ozonolysis of the enol acetate. Furthermore, no enol acetate could be obtained from acetophenone. These facts indicate that enolization does not take place from the methyl hydrogen under the experimental conditions employed.

The synthesis of 1-bromoketones from methyl ketones has been accomplished by bromination and hydrolysis of α-alkyl vinyl acetates.[9]

In the present investigation, a mixture of the ketone, acetic anhydride and *p*-toluenesulfonic acid was boiled for four to ten hours and the acetic acid formed during the reaction was distilled off. The yields of enol acetate obtained from the three compounds under consideration were 32–68%, the balance of the product being largely the unreacted ketone.

Upon addition of bromine to the enol acetate in cold carbon tetrachloride solution, bromine is absorbed quantitatively. Excess bromine, however, causes substitution with evolution of hydrobromic acid. This is undoubtedly due to the ease of elimination of the tertiary bromine. On adding the brominated mixture to methyl alcohol (99.5–100%), hydrolysis takes place because of the presence of a halogen and an ester grouping on the same carbon atom, resulting in the formation of α-bromoketones in 46–90% yields.

Taking methyl *n*-amyl ketone as an example, the reaction involved is as follows



$$C_4H_9CH_2COCH_3 + (CH_3CO)_2O\ (p\text{-tol. sulf. acid}) \longrightarrow C_4H_9CH{=}\underset{\displaystyle OCOCH_3}{\underset{|}{C}}CH_3 + CH_3\dot{C}OOH$$

$$\Big\downarrow Br_2\ (\text{In } CCl_4)$$

$$CH_3OCOCH_3 + HBr + C_4H_9CHBrCOCH_3 \xleftarrow{CH_3OH} C_4H_9CHBr\underset{\displaystyle OCOCH_3}{\underset{|}{C}}BrCH_3$$

The reaction seems to be of general applicability to the synthesis of α-bromoketones where the presence of a methylenic hydrogen will permit the formation of an enol acetate.

Experimental Part

The experimental procedures in the preparation of the three bromoketones followed a general pattern and a description applicable to all three is given below. The quantities involved together with pertinent data are given in a separate table.

Preparation of Enol Acetate.—The ketone was distilled at atmospheric pressure and the pure fraction taken for the preparation of the enol acetate. A suitable amount of the ketone was added to a mixture of acetic anhydride and *p*-toluenesulfonic acid and heated for a specified period. During the heating period, acetic acid along with some

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(2) Bedoukian, THIS JOURNAL, **66**, 1325 (1944).

(3) Hancu, *Ber.*, **42**, 1052 (1909).

(4) Mannich and Hancu, *ibid.*, **41**, 564 (1908).

(5) H. Schmidt, Schimmel & Co. Annual Reports, 124–126 (1938).

(6) Gwynn and Degering, THIS JOURNAL, **64**, 2216 (1942).

(7) Hennion and Nieuwland, *ibid.*, **56**, 1802 (1934).

(8) Faworsky and co-workers, *J. prakt. Chem.*, **2**, 88, 641 (1913); Bachmann and Hill, THIS JOURNAL, **56**, 2730 (1934); Temnikova and Veksler, *J. Gen. Chem.* (U.S.S.R.), **11**, 3 (1941); *C. A.*, **35**, 5459 (1941).

(9) Slanina, Hennion and Nieuwland, THIS JOURNAL, **58**, 891 (1936).

acetic anhydride was allowed to distill off, care being taken to keep the distillation temperature below 125° in order to avoid excessive losses of acetic anhydride. The residue was then washed several times with water and finally with 5% sodium carbonate to remove any acid present. The crude enol acetate was fractionated through a three-foot Whitmore–Fenske type column to obtain the pure enol acetate.

Bromination of Enol Acetate.—The enol acetate was dissolved in twice its volume of carbon tetrachloride and cooled in an ice-bath. The required theoretical quantity of bromine dissolved in an equal volume of carbon tetrachloride was then added slowly to this mixture from a buret with constant shaking, care being taken not to allow the temperature of the mixture to rise above 10°.

Formation of α-Bromoketone.—The brominated mixture was added to an equal volume of methyl alcohol (99.5–100%) with cooling and allowed to stand for two days. The mixture was then diluted with an equal volume of water and the separated oil washed with 5% sodium carbonate to remove any acid present. The carbon tetrachloride was distilled off at atmospheric pressure and the residue distilled under vacuum to yield the α-bromoketone.

TABLE I

EXPERIMENTAL CONDITIONS AND PROPERTIES OF COMPOUNDS INVESTIGATED

	Cyclohexanone	Propiophenone	Methyl *n*-amyl ketone
B. p. of ketone, °C.	155–156	216–217	150–151
$(CH_3CO)_2O$ used per mole of ketone, moles	2	2.5	2
p-Tol. sulf. acid per mole of ketone, g.	1	5	5
Time of heating, hrs.	4	6	10
Yield of enol acetate, %	68	47	32
B. p. of enol acetate (17 mm.), °C.	74–76	133–136	75–76
$n^{25}D$ of enol acetate	1.4585	1.5334	1.4270
d^{25}_4 of enol acetate	1.002	1.046	0.8830
Bromoketone yield from enol acetate, %	46	90	66
B. p. of bromoketone (20 mm.), °C.	112–113	138–139	87–88
$n^{25}D$ of bromoketone	1.5085	1.5686	1.4620
d^{25}_4 of bromoketone	1.340	1.405	1.240

Cyclohexanone.—The enol acetate[10] of cyclohexanone and monobromocyclohexanone[11] have been prepared previously.

Propiophenone.—The enol acetate prepared for the first time is an oil having a strong lemon yellow color.

Anal.[12] Calcd. for $C_{11}H_{12}O_2$: C, 75.01; H, 6.86. Found: C, 74.92; H, 6.73. The bromoketone[13] has been previously reported.

Methyl *n*-Amyl Ketone.—The enol acetate prepared for the first time is a liquid possessing a fruity odor.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.17; H, 10.33. Found: C, 68.95; H, 10.64.

The bromoketone (3-bromoheptanone-2)[14] has been reported previously.

Ozonolysis of the Enol Acetate of Methyl *n*-Amyl Ketone.[15]—A 5.3-g. sample of the enol acetate was dissolved in 170 ml. of pure redistilled chloroform and ozonized at 0° with approximately 50% excess ozone. The ozonide was decomposed with zinc (5 g.) and acetic acid (20 g.)–water (20 g.) mixture in the ordinary manner. After thorough shaking the acetic acid–water layer was drawn off and the chloroform solution further extracted with 20 ml. of water. The two aqueous extracts were combined.

Ten ml. of the aqueous solution was added to a mixture of 90 ml. of ethyl alcohol containing 0.5 g. of 2,4-dinitrophenylhydrazine and boiled for five minutes. No derivative of formaldehyde could be obtained from this solution. An identical acetic acid–water solution containing 10 mg. of formaldehyde gave a substantial quantity of formaldehyde 2,4-dinitrophenylhydrazone (m. p. 166°). There was thus no appreciable quantity of formaldehyde formed during ozonolysis, proving the absence of any enol acetate formation from the methyl hydrogen.

One-tenth of the chloroform solution was taken and 2,4-dinitrophenylhydrazone derivative prepared from it in the ordinary manner. The orange yellow crystals obtained were recrystallized from ethyl alcohol and had a m. p. of 106°. This derivative did not give a depression in m. p. when mixed with the 2,4-dinitrophenylhydrazone of a known sample of *n*-valeraldehyde. The presence of *n*-valeraldehyde proved the formation of enol acetate from the methylenic hydrogen.

The remaining nine-tenths of the chloroform solution was extracted twice with 50-ml. portions of 10% sodium carbonate solution. The alkaline solution was filtered and acidified with 10% sulfuric acid solution. No separation of oil resulted. The acid solution was ether extracted and the ether distilled off at atmospheric pressure. The absence of any residue showed that there was no caproic acid present, proving again that no formation of enol acetate took place from the methyl hydrogen.

Summary

A general method has been developed for the preparation of ketone enol acetates, applicable to ketones possessing a methylenic hydrogen. Bromination of these enol acetates with subsequent hydrolysis in methyl alcohol gives α-bromoketones in good yields.

Cyclohexanone, propiophenone and methyl *n*-amyl ketone were considered representative of various types of ketones and were chosen to test the general applicability of this procedure. The yield of enol acetates ranged from 32–68% and α-bromoketones were obtained from these in 46–90% yields.

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[10] Hücke land Radszat, *J. prakt. Chem.*, **140**, 247 (1934).

[11] Kotz, *Ann.*, **358**, 195 (1908).

[12] The author is greatly indebted for the analyses to Mrs. D. Jewitt and Dr. G. A. Grant, of the Research Laboratories of Ayerst, McKenna and Harrison, Montreal, Canada.

[13] Higginbotham, Lapworth and Simpson, *J. Chem. Soc.*, **125**, 2339 (1924).

[14] Bachmann and Hill, THIS JOURNAL, **56**, 2730 (1934).

[15] The author is greatly indebted for the ozonolysis to Miss Dorothy Lawrence of the Research Laboratories of Charles E. Frosst Co., Ltd., Montreal, Canada