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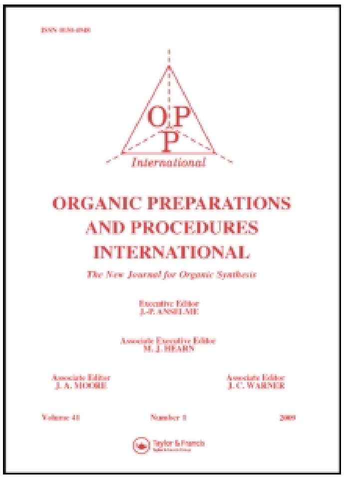

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BROMINATION OF UNSYMMETRICAL KETONES WITH CUPRIC BROMIDE. PRODUCT DEPENDENCE ON REACTION CONDITIONS

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BROMINATION OF UNSYMMETRICAL KETONES WITH CUPRIC BROMIDE. PRODUCT DEPENDENCE ON REACTION CONDITIONS.

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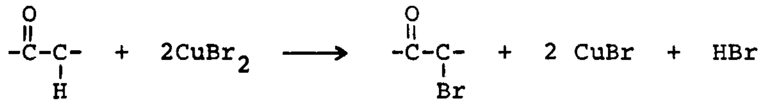
The use of cupric bromide for the α-halogenation of ketones has many advantages.[1] The yields are usually high, and isolation of the product is generally simple. Common groups such as phenyl and substituted phenyl, ester, olefin and cyano are generally not attacked under the usual reaction conditions and do not interfere with the progress of the reaction. To our knowledge, systematic investigations of the bromination of unsymmetrical ketones with cupric bromide which contain replaceable hydrogens at both α-positions have not been reported. We now describe the ratios of products obtained from the ketones of series I under a variety of experimental conditions.

$PhCH_2COCHR_1R_2$

I

a) $R_1 = R_2 = H$
b) $R_1 = H;\ R_2 = CH_3$
c) $R_1 = R_2 = CH_3$

Prior to 1964, a number of reaction conditions had been reported for $CuBr_2$ halogenations of ketones. In 1964, King and Ostrum published an improved procedure using a slurry of $CuBr_2$ in $CHCl_3$-EtOAc at reflux.[2] It was suggested that the reaction proceeds according to equation 1. The authors



$$-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle H}{|}}{C}- \; + \; 2CuBr_2 \longrightarrow -\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle Br}{|}}{C}- \; + \; 2\,CuBr \; + \; HBr \qquad (1)$$

claimed that HBr is only slightly soluble in the refluxing solvent mixture and escapes as formed. This would constitute a major advantage since HBr is known to catalyze the isomerization and disproportionation of α-bromoketones.[3]

Our initial studies of this procedure used equimolar quantities of $CuBr_2$ and ketone (100% excess of ketone). Under these conditions, the amount of dihalogenation was found to generally be less than 2%. The use of an excess of ketone was to insure that the ratio of monohalogenated products formed would not be altered by preferential removal of one product during the second halogenation step. The stoichiometry shown in equation 1 was not followed. Generally, between one and two moles of $CuBr_2$ reacted with one mole of ketone. This suggested that not all the HBr is being immediately expelled as formed, and in the presence of CuBr and air, $CuBr_2$ is being regenerated. This raised the question of whether the observed ratios of products were being determined kinetically, or whether the HBr which might be present was causing isomerization of initally-formed products. If the latter were the case, proper choice of reaction conditions might allow one to control the ratio of products. To investigate this further, we followed two lines of approach: (1) Lower reaction temperatures in order to slow down the isomerization reactions. (2) Removal of the HBr as it is formed by conducting the reaction under an oxygen atmosphere, thus taking advantage of the possibility that the CuBr and HBr formed do react with oxygen. Our results are presented in Table I.[4]

Table I

Ratio of Products ($PhCH_2COCBrR_1R_2/PhCHBrCOCHR_1R_2$)[a]

	In Air[b]			In O_2[c]	
Substrate	Reflux	Room Temp.	0°	Room Temp.	0°
Ia	$\frac{1}{5.5}$	$\frac{1}{7}$	$\frac{1}{36}$	$\frac{\text{none}^d}{\text{all}}$	$\frac{\text{none}^d}{\text{all}}$
Ib	$\frac{5.3}{1}$	$\frac{2.3}{1}$	$\frac{1.5}{1}$	$\frac{1.3^e}{1}$	$\frac{1^f}{2.8}$
Ic	$\frac{\text{all}}{\text{none}}$	$\frac{\text{all}}{\text{none}}$	$\frac{7.5}{1}$	$\frac{2.4^g}{1}$	$\frac{1^g}{2.2}$

a) Monobrominated products. b) All reactions were performed in 1:1 $CHCl_3$-EtOAc using equimolar amounts of $CuBr_2$ and ketone. c) All reactions were performed in EtOAc using equimolar amounts of $CuBr_2$ and ketone. Selected reactions were repeated in 1:1 $CHCl_3$-EtOAc with essentially identical results. d) The crude product was essentially pure 1-bromo-1-phenyl-2-propanone. A trace of starting material remained. e) The crude product consisted of approximately 20% starting material, 70% monobrominated material, and 10% dibrominated material. f) The crude product consisted of approximately 11% starting material, 80% monobrominated material, and 9% dibrominated material. g) The crude product consisted of approximately 5% starting material, 93% monobrominated material, and 2% dibrominated material.

The temperature dependence of the product ratios was established as being due to the isomerization of initially-formed products for reactions conducted in air as follows. Brominations initially conducted at 0°, were heated at reflux for 10-30 minutes before workup and analysis. In each case the ratio of products was identical to that observed from the same bromination reaction at reflux. Similar experiments at 0°, followed by allowing the reactions to remain at room temperature for 24 hours before workup and analysis, led to product ratios intermediate between those found at room temperature and at 0°. Apparently, isomerization also occurs at room temperature, but at a slower rate than at reflux.

For reactions conducted under an air atmosphere, generally more than one mole but less than two moles of $CuBr_2$ reacted with one mole of ketone. Under an oxygen atmosphere, 1 mole of $CuBr_2$ led to two bromination reactions. Under a nitrogen atmosphere, the stoichiometry of equation 1 was observed for the reaction of Ia, the only compound of series I tested in this manner. Based upon these results and the fact that the ratios of products under an oxygen atmosphere continue the trends observed by lowering the temperature of the reaction, we attribute the role of oxygen to the prevention of isomerization by the removal of the HBr as formed. Since the ratios of products under an oxygen atmosphere are also temperature dependent, removal of HBr and isomerization apparently are competitive, at least at room temperature.

In conclusion, the results presented herein[4] indicate that a significant measure of control over the ratio of bromination products can be obtained by varying the reaction temperature and the reaction atmosphere. For synthetic purposes, the effect of these factors should be explored in order to maximize the yield of the desired bromination product.

EXPERIMENTAL

General Halogenation Procedure.- A mixture of 0.01 mole cupric bromide, 8 ml. $CHCl_3$, and 8 ml. EtOAc was placed in a 50-ml. three-necked flask, which contained a magnetic stirring bar. After the desired atmosphere and temperature conditions were established, 0.01 mole of ketone in 4 ml. of 1:1 $CHCl_3$-EtOAc was added. A pressure-equalizing addition funnel was used in the case of an oxygen or a nitrogen atmosphere. Rapid stirring was maintained throughout the reaction.

The completed reaction mixture was brought to room temperature, filtered with suction, and the filtrate evaporated to dryness under a vacuum at a bath temperature below 30°. Approximately 20 ml. of CCl_4 was added to the residue, and the filtration and evaporation procedure was repeated to remove small amounts of residual copper salts.

The completion of the reaction is indicated by the formation of light colored copper salts from the black $CuBr_2$. Reaction times were affected by the reaction temperature, but relatively little by the ketone used. For example, at reflux, ketones Ia-Ic all reacted within 30-50 minutes. At 0°, 15-20 hours were usually required.

Analyses of the reaction products were accomplished by nmr spectroscopy on the evaporated reaction mixtures using the following peaks ($\delta^{CCl_4}_{TMS}$): $PhC\underline{H}_2COCH_3$ (3.58, s), $PhC\underline{H}BrCOCH_3$ (5.45, s), $PhC\underline{H}_2COC\underline{H}_2Br$ (3.81, s); $PhC\underline{H}_2COCH_2CH_3$ (3.56, s), $PhC\underline{H}BrCOCH_2CH_3$ (5.39, s), $PhC\underline{H}_2COCHBrCH_3$ (3.90, s); $PhC\underline{H}_2COCH(CH_3)_2$ (3.62, s), $PhC\underline{H}BrCOCH(CH_3)_2$ (5.58, s), $PhC\underline{H}_2COCBr(CH_3)_2$ (4.03, s).

Solvent Effects.- During the early stages of this work, a variety of solvents were tried, at reflux, for the bromination of Ia. The solvent did not have a great influence on the ratio of products, but did greatly affect the reaction time. Non-polar solvents required long reaction time, e.g., C_6H_6 3 hours 45 minutes, $CHCl_3$ 2 hours 45 minutes. For all practical purposes, EtOAc is equivalent to 1:1 EtOAc-$CHCl_3$, which was used in most of this work. Ether solvents greatly accelerated the reaction. In THF or $CH_3OCH_2CH_2OCH_3$, the reaction was complete in less than 15 minutes. However, reaction between the solvent and the liberated HBr seemed to occur, as evidenced by nmr peaks in the CHBr region. For low temperature brominations, $CH_3OCH_2CH_2OCH_3$ is probably the solvent of choice.

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