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A SIMPLE AND CONVENIENT SYNTHESIS OF β-HALOKETONES

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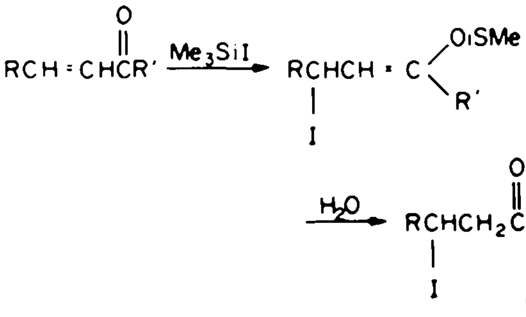
Abstract- A new rapid quantitative method to synthesize β-halo-ketones is described (eqn 2) which utilizes the reaction of an enone with a tetraalkyl ammonium halide in anhydrous trifluoro acetic acid. The method is especially convenient for the preparation of β-iodoketones.

β-Haloketones are a useful class of synthetic intermediates, which undergo a number of substitution reactions at halogen, as well as protection and addition reactions at the CO group.[1] The synthesis of this type of compound is often instantaneous from the addition of anhydrous HX (X = Cl, Br, I) to the corresponding enone, neat or in an inert solvent.[2] The reaction is not experimentally convenient for HI, however, due to the expense of the pure gas or the inconvenience of preparing it in the laboratory.

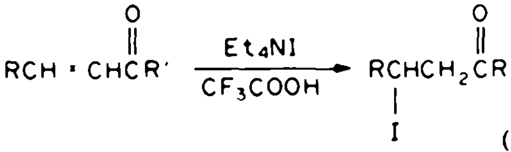
In a recent report, Miller and McKean[3] reported a new procedure to prepare β-iodoketones. Their method (eqn 1) utilizes the low temperature 1,4-addition of trimethylsilyliodide to enones to give the intermediate iodo TMS enol ethers, and the ready hydrolysis of these to the β-iodo ketones. The reaction gives good yields, but requires the use of the highly reactive, moisture sensitive, and expensive reagent, trimethylsilyl iodide. These authors imply that the simple addition of HI to the enones is not a satisfactory process.



$$RCH{=}CH\overset{O}{\overset{\|}{C}}R' \xrightarrow{Me_3SiI} \underset{I}{\underset{|}{RCH}}CH{=}C\begin{smallmatrix}OiSMe\\R'\end{smallmatrix} \xrightarrow{H_2O} \underset{I}{\underset{|}{RCH}}CH_2\overset{O}{\overset{\|}{C}}R' \qquad (1)$$

We had previously reported the results of a systematic investigation of the reaction of HCl, HBr, and HI gas with enones and related compounds.[2] This study showed that the hydrogen halides form stable salts with some enones, such as β-substituted cyclohexenones, for which the addition products are too unstable to be formed. However, most enones add rapidly and quantitatively when treated with the hydrogen halides, and HI is the most reactive. Miller and McKean evidently overlooked our report.

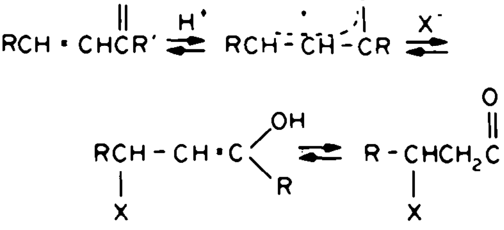
Because of the experimental difficulties inherent in either of these recorded procedures, we have sought a new method to prepare β-iodoketones. We have found that tetraalkyl ammonium iodides react with enones in trifluoroacetic acid at room temperature to give the β-iodoketones as the only detectable products. The reaction is conveniently monitored by NMR spectroscopy, and is usually complete in less than one minute. Simple extraction with pentane and washing with water give the β-iodoketones in essentially pure form. The analogous reaction also works to prepare β-bromo- and β-chloroketones in some cases.



$$RCH{=}CH\overset{O}{\overset{\|}{C}}R' \xrightarrow[CF_3COOH]{Et_4NI} \underset{I}{\underset{|}{RCH}}CH_2\overset{O}{\overset{\|}{C}}R' \qquad (2)$$

The reaction of Et_4NX/CF_3COOH with some simple enones, of several structural types, is recorded in Table 1.

The mechanism of the reaction appears to be as shown in eqn (3). It is known that CF_3COOH is a fairly non-nucleophilic acid which is strong enough to protonate enones to an equilibrium extent readily detectable by NMR spectroscopy (deshielding of the NMR proton signals in the cation as compared to the enone.)[4] Tetraalkyl ammonium halides are very soluble in CF_3COOH, and thus provide a convenient source of X to trap the cation and give the enol, which subsequently tautomerizes.



$$RCH{=}CH\overset{O}{\overset{\|}{C}}R' \overset{H^+}{\rightleftharpoons} RC\overset{+}{H}{-}\overset{+}{C}H{-}\overset{OH}{C}R \overset{X^-}{\rightleftharpoons} \underset{X}{\underset{|}{RCH}}-CH{=}C\begin{smallmatrix}OH\\R\end{smallmatrix} \rightleftharpoons R-\underset{X}{\underset{|}{CH}}CH_2\overset{O}{\overset{\|}{C}}-R' \qquad (3)$$

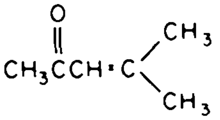
One major side reaction appears possible under the experimental conditions, the trapping of the cation with CF_3COO to give a β-tri-fluoracetoxy ketone. Control experiments demonstrated that only protonation occurs, and there is no addition, even after several days at room temperature, except for the most reactive enones. Among the entries in Table 1, only methyl vinyl ketone added CF_3COOH, and even in this case halide addition was fast enough to overshadow this reaction.

The rate of reaction shows a dramatic effect on the halide used. The reaction is very fast for tetraalkyl ammonium iodides, but always slower for the bromides and still slower for the chlorides. In some cases

Table 1. Reaction of Et_4NX in CF_3COOH with enones

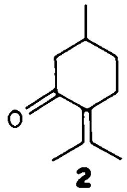
Starting Enone		Yields of β-Haloketones			NMR Data for the β-Iodoketones
Number	Name	X = I	X = Br	X = Cl	
1	mesityl oxide	95%[a,c]	75%[b,c]	60%[b,c]	δ 2.15 (6H, s), 2.20 (3H, s), 3.16 (2H, s).
2	pulegone	97%[a,c]	93%[a,c]	60%[b,c]	δ 0.98 (3H, d, J=6 Hz), 2.00 (3H, s), 2.20 (3H, s), 1.6–2.7 (7H, m).
3	cyclohexenone	85%[a,c]	50%[b,c]	35%[b,c]	δ 1.7–2.7 (6H, m), 2.09 (1H, d, J=9 Hz), 3.07 (1H, J=4 Hz), 4.50 (1H, v br).
4	4,4-dimethyl cyclohexenone	95%[a,c]	50%[b,c]	35%[b,c]	δ 1.17 (3H, s), 1.20 (3H, s), 1.8–2.7 (4H, m), 3.05 (dd, J=7,8 Hz), 4.35 (dd, J=7,8 Hz).
5	cyclopentenone	50%[b]	0%[b,d]	0%[b,d]	δ 2.3–2.9 (6H, m), 4.65 (1H, v br).
6	methyl vinyl ketone	95%[a]	42%[a]	35%[a]	δ 2.18 (3H, s), 3.18 (4H, br s).
7	3-methylene-2-norbornanone	97%[a]	93%[a]	90%[a]	δ 1.6–2.3 (6H, m), 2.3–3.0 (3H, m), 3.0–3.8 (2H, m).

a. Isolated yields. Remainder lost in the work-up procedure. NMR spectroscopy shows a quantitative reaction.
b. Product ratio determined in solution. Remainder is starting material. These ratios vary with the amount of Et_4NX used, and reflect the values with 2.5 equivalents of reagent.
c. Products are very sensitive to elimination of HX.
d. Cyclopentenone does not react with HBr or HCl gas.[2]



$CH_3\overset{\overset{O}{\|}}{C}CH{=}C(CH_3)_2$

1



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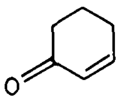

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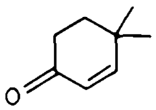

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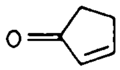

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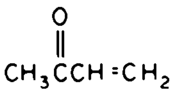
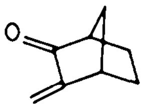


$CH_3\overset{\overset{O}{\|}}{C}CH{=}CH_2$

6



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the chlorides and even the bromides did not react. The fluorides failed to react in all cases investigated.

The reaction is also adversely affected by the presence of water, so the tetraalkyl ammonium halides and CF_3COOH must be dried before use. Deliberate addition of water caused the reaction to stop short of completion, and a stable mixture of starting enone and β-haloketone was formed. The ratio increased toward starting material as more water was added, but no stoichiometric relationship appeared evident.

These results suggest that hydrogen bonding to the halide ion (Cl > Br > I) by CF_3COOH decreases the ease of the second step in the mechanism (in the case of F , complete proton transfer to give HF presumably occurs). Stronger hydrogen bonding of X to H_2O either blocks the second step or at least adversely affects the position of equilibrium. Addition of a large excess of H_2O to the CF_3COOH reaction solution caused complete reversion of the reaction to the enones in sensitive cases, such as cyclohexenone.

That an equilibrium is involved was further demonstrated with mesityl oxide. Treatment of this compound with one equivalent each of Et_4NI and Et_4NBr in CF_3COOH gave a 95:5 ratio of the iodo to bromo ketone. This ratio changed to *ca* 90:10 with time. The same ratio was also reached by allowing the preformed iodo or bromo ketone to react with the other R_4NX species in CF_3COOH. This reaction is assumed to involve an elimination–addition sequence, though none of the enone was detectable by NMR spectroscopy.

Because of the sensitivity of many of the β-haloketones toward elimination, the work-up conditions were crucial. In some cases, extraction with pentane, filtration through $MgSO_4$, and removal of the pentane *in vacuo* gave the β-haloketone in essentially pure form, though most products could be washed briefly with water.

The addition reaction was investigated for a number of compounds not listed in Table 1. The reaction failed for the 3-substituted cyclohexenones and cyclopentenones which were previously shown not to add HX directly.[2] In addition several simple α,β-unsaturated esters, amides, and nitriles, as well as unactivated alkenes, were shown to be inert to the reaction conditions. Even the addition of a catalytic amount of H_2SO_4 gave the starting materials unchanged.

The reaction with methacrolein was more complex; uncharacterized products not containing an aldehyde function were formed. Dibenzalacetone gave the known orange HX salts.[5] Phenyl propenyl ketone gave an immediate complex precipitate which may have been polymeric. 2-Carbomethooxycyclopentenone[6] gave a polymer, which is not surprising for this highly reactive compound. 4,4-Dimethylcyclohexadienone gave only protonation and slow dienone-phenol rearrangement.[4] Thus, the reaction appears to be useful and selective for formation of simple β-haloketones.

Some attempts were made to substitute other acids and halide sources, to make the procedure cheaper. Sodium and potassium halides are too insoluble in CF_3COOH to be effective.† Use of a co-solvent with stoichiometric CF_3COOH was unsuccessful in all cases investigated, either because the solvent was too non-polar to dissolve R_4NX or too nucleophilic to remain inert in the system. Acetonitrile did dissolve everything but no reaction occurred, presumably because the equilibrium reaction is too unfavorable under the dilute conditions. Other common acids appear to be too mucleophilic to leave the enones unchanged or else can not be obtained in anhydrous form.

The experimental convenience and the commercial availability of the reagents appear to make this procedure the method of choice to prepare β-iodoketones. In most cases, the superior method to form β-chloro and β-bromoketones is probably by reaction of the enones with gaseous HCl or HBr, though the present method does offer a milder method which may have some applications.

It is interesting to note that a solution of Et_4NI in CF_3COOH which is not rigorously protected from O_2 and light slowly begins to deposit glistening purple black crystals after a few hours. This product has been identified as Et_4NI_3 . This ionic compound is completely insoluble in H_2O! The present seredipitious synthesis is simpler than the recorded synthesis of this compound.[7]

EXPERIMENTAL

Trifluoroacetic acid was purified by distillation under N_2. The center fraction b.p. 71 72 (corr) was collected and stored under N_2 in a glass flask fitted with a siphoning head made with teflon stopcocks. Pentane was distilled before use. Et_4NBr and Et_4NCl were dried and stored at 120 prior to use. Et_4NI and all enones were used as supplied by the manufactures.

NMR spectra were recorded on a Varian EM-360 spectrometer in CCl_4 for isolated products (Table 1) or in CF_3COOH for solution data.

In a typical procedure, 0.630 g of Et_4NI and 0.180 g of mesityl oxide were weighed in an NMR tube, then *ca* 2 ml of CF_3COOH was added. An NMR scan revealed no starting material remained after 1 min. The contents of the tube were poured into pentane-H_2O and extracted rapidly. The pentane layer was separated, filtered through solid $MgSO_4$, and the solvent removed at the rotary evaporator at ambient temperature. The remaining yellow oil (0.396 g, 95%) showed only peaks for 4-methyl-4-iodo-2-pentanone (Table 1) by NMR spectroscopy. Prolonged contact with water or exposure of the product to the conditions of the rotary evaporator caused product losses due to reversion to starting materials.

In some cases, (i.e. pulegone) the product was even more sensitive to H_2O, and the isolation procedure consisted simply of extraction of the CF_3COOH solution with pentane and removal of the pentane on the evaporator.

The reactions were conveniently monitored by NMR spectroscopy in all cases. Required reaction times varied from too fast to measure to several hours at ambient temp. All products had NMR spectra identical to the ones from the reaction of the enone with HX.[2]

Studies of reaction variables were carried out mainly with mesityl oxide. This compound has a vinyl signal at $\delta 6.31$ in CF_3COOH, and the products have a gem-dimethyl signal at $\delta 2.12$ for $X = I$, $\delta 1.91$ for $X = Br$ and $\delta 1.72$ for $X = Cl$, which is easily detectable in the presence of excess Et_4NX.

Any NMR tube containing Et_4NI in CF_3COOH which was allowed to stand overnight deposited glistening purple–black needles, unless it was protected from light. A flask of Et_4NI in CF_3COOH which was allowed to stand open overnight in the hood gave a 90% yield of the compound, Et_4NI_3, which was collected and washed with H_2O, m.p. 138-140 (lit. 142 ,[7] 139-141)[8].

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†Lithium halides are soluble in CF_3COOH, but offer no price advantage. They do give the β-haloketones, though preliminary work suggests some reactivity differences. A comparison study of Et_4NX and LiX as the halide source in this reaction will be reported later.