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REDUCTION OF α,α'-DIBROMO KETONES BY ULTRASONICALLY DISPERSED MERCURY IN PROTIC SOLVENTS

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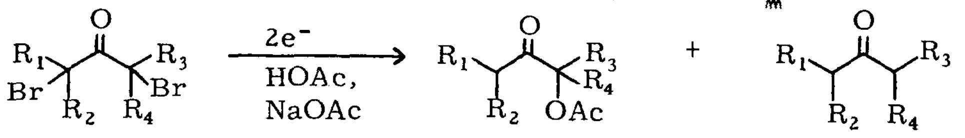
We recently reported a study of the electrochemical reduction of α,α'-dibromo ketones (**1**) in acetic acid-sodium acetate.[1] With highly substituted dibromo ketones (at least three of the groups R_1-R_4 = alkyl) excellent yields of α-acetoxy ketones (**2**) were obtained, while less highly substituted dibromides led to the so-called "parent" ketone (**3**). A number of synthetically attractive features are associated with this reductive substitution (**1**→**2**): (a) it nicely complements conventional oxidative routes[2] to α-acetoxy ketones, which are generally better for the synthesis of less highly substituted acetoxy ketones; (b) only a single acetoxy group is introduced; (c) in principle it should be possible to introduce a wide variety of nucleophiles alpha to the carbonyl group, since acetoxy ketones **2** apparently arise by nucleophilic attack of acetic acid or acetate upon an intermediate 2-hydroxyallyl cation (**4**).[1] We have recently been engaged in extending our original work in a variety of directions aimed at exploring the synthetic utility of reductive substitution on α,α'-dibromo ketones. We now wish to report that dibromo ketones **1** can also be converted to products **2** and **3** by the action of mercury in acetic acid. It has been reported that non-benzylic dibromo ketones are not reducible by mercury.[3] This, however, is a kinetic phenomenon. We find that **1** is converted to **2** and **3** at a convenient rate by mercury if the mercury is in a finely dispersed state, which we most commonly achieve by placing a solution of **1** in acetic acid (or other protic solvent) with a small amount of mercury in a water-filled laboratory ultrasonic cleaner thermostatted at 25°C. A series of dibromo ketones (**5**-**11**) were reduced by this procedure. They included 2,4-dimethyl-2,4-dibromo-3-pentanone (**5**), 1,3-dibromo-3-methyl-2-pentanone (**6**), 2,4-dibromo-2-methyl-3-pentanone (**7**), 2,4-dibromo-2-methyl-3-heptanone (**8**), 2,4-dibromo-2,5-dimethyl-3-hexanone (**9**), 2,6-dibromo-2-methylcyclohexanone (**10**), and 4,6-dibromo-5-nonanone (**11**). The results are summarized in



1 **2** **3** (1)

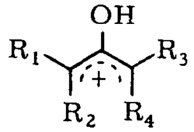


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Table I. In most reactions 2 and 3 constituted >90% of the acetic acid-soluble product (see Experimental), but a few reactions formed significant amounts of other substances. The reduction of dibromo ketones by mercury differs in two significant respects from the electrochemical reduction: (a) the ratio of 2 to 3 is always higher for a given dibromo ketone in the mercury reaction than in the electrochemical reaction; and (b) the total yield of products (material balance) is generally lower in the mercury reaction than in the electrochemical reaction. When the carbon skeleton of 1 is unsymmetrical, two isomeric acetoxy ketones ought to be formed. This was usually the case (Table II). It is interesting to note that increasing the bulk of the carboxylic acid favors substitution at the tertiary site of the ketone (cf. the two experiments on 8 and 9 in Table II). This effect is general and will be reported upon separately when an extensive study of it now under way in our laboratory is complete.[4a] We wish, however, to point out at this time the fact that by proper choice of carboxylic acid it is usually possible to effect regioselective α-substitution on an unsymmetrical ketone, a feature of synthetic interest.

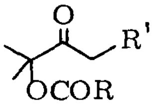
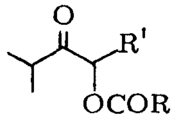
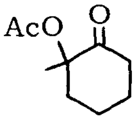
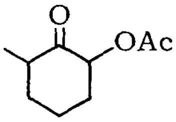
Table I. Reduction of dibromo ketones by mercury.

Dibromide	Solvent	Yields, %[a] α-Substituted Ketone	Parent Ketone	Other
5	AcOH	71	0	0
5	Me_3CCO_2H	75	0	0
5	$EtCO_2H$	80	0	0
5	AcOD	60[b]	0	0
5	MeOH	71	0	0
6	AcOH	31[c]	4	3
7	AcOH	68[c]	0	0
8	AcOH	75[c]	0	0
8	Me_3CCO_2H	74[c]	0	0
9	AcOH	60[c]	0	0
9	Et_3CCO_2H	76[c]	0	0
10	AcOH	66[c]	1	18[d]
11	AcOH	35	10	5[e]

[a] Yields of products soluble in acetic acid. [b] Product is α-deutero-α'-acetoxy ketone. [c] For isomer ratios, see Table II. [d] Four minor products, vpc retention times shorter than 2 or 3. [e] Monobromo ketone.

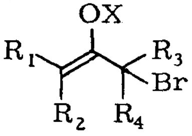
The mercury reaction seems mechanistically very similar to the electrochemical reductive substitution previously reported[1] by us: increasing alkyl substitution in 1 favors formation of 2, and the ratio of isomeric acetoxy ketones from unsymmetrical dibromides is the

Table II. Isomer ratios in reductions of unsymmetrical dibromides.

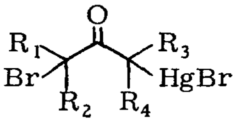
Dibromide	Solvent	Relative yields, %	
			
6	$MeCO_2H$	70	30
7	$MeCO_2H$	55	45
8	$MeCO_2H$	70	30
8	Me_3CCO_2H	96	4
9	$MeCO_2H$	93	7
9	Et_3CCO_2H	100	0
			
10	$MeCO_2H$	44	56[a]

[a] 32% cis and 24% trans.

same whether 1 is reduced electrochemically or by mercury. Yet, the two reactions are not mechanistically identical, since the ratio of 2 to 3 is usually higher, and total yields are lower, in the mercury reaction.[1,4] We believe[1] that 2 arises by ionization of an enol bromide



12a, X = H
b, X = HgBr



12 to an allylic cation, and 3 by tautomerization of 12. Tautomerization of 12b should be slower than that of 12a because of the need to cleave an O—Hg bond; this would favor formation of 2. The lower total yields could well be due to formation of insoluble C—Hg products, eg., 13.

The fact that metallic mercury can reduce dibromo ketones may seem surprising, if one notes the following potentials:

$Hg(II) + 2e^- \rightarrow Hg^\circ \qquad \Delta E^\circ = +0.85V(N.H.E.)^5$

$BrCH_2COCH_3 + 2e^- \rightarrow {}^-CH_2COCH_3 + Br^- \qquad E_{1/2} = -0.10V(N.H.E.)^6$

Net: $Hg^\circ + BrCH_2COCH_3 \rightarrow Hg(II) + {}^-CH_2COCH_3 + Br^- \; \Delta E = -0.95V \qquad (2)$

Since a negative ΔE corresponds to an endothermic reaction, it would appear at first sight that it should not be possible to reduce bromo ketones (and dibromo ketones, which have similar reduction potentials) by mercury. However, there are three major effects which are neglected when potentials are compared in this way, and all three act in the direction to favor reduction. First, the reduction potential cited for bromoacetone is a polarographic half-wave potential,[6] but since reduction of alkyl halides is totally irreversible electrochemically, E° for the reduction of bromoacetone is positive of the observed $E_{1/2}$ (by some unknown amount).[7] Secondly, the potential for oxidation of mercury in the presence of bromide, a coordinating anion, will be negative of the above value, particularly in the low dielectric constant carboxylic acids ($\epsilon_{HOAc} = 6$) used for most of the present study. Finally, and related to the latter, coordination of mercury to the enolate ion as in **12b** will also shift the oxidation potential of mercury negative from the literature value. These effects should not be small. Polarographically, the anodic dissolution of mercury is shifted approximately 0.4V negative in the presence of either bromide or hydroxide ions,[8,9] and since enolate ions are softer bases and hence presumably better ligands than hydroxide, the negative shift induced by coordination of Hg(II) to the enolate is presumably even greater. Thus, it is not at all unreasonable that mercury should be capable of reducing dibromo ketones.

Experimental procedure--A 10 ml. erlenmeyer flask containing 5 mmol. of dibromide, 5 ml. of solvent, and 2-3 ml. of mercury was placed in an 80-watt ultrasonic cleaner for 1-4 days.[10] After reaction was complete insoluble materials were removed by centrifugation and the solution worked up as described[1] previously. Products were both analyzed and separated for nmr and mass spectral identification by vpc.

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9. The data cited[8] are for oxidation of mercury to Hg(I), but the effect will be of similar magnitude or greater with Hg(II), which is a better coordinating anion than Hg(I).

10. The reaction may be followed by tlc, nmr, or vpc. Reactions are faster with the better mercury dispersions available using a high-speed laboratory homogenizer (Dr. Jan Andersson, unpublished work).