COPPER-CATALYZED OXYGENATION OF BRANCHED ALDEHYDES -- AN EFFICIENT KETONE SYNTHESIS

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Molecular oxygen as an oxidizing agent is becoming increasingly important in organic synthesis. We have investigated the oxygenation of α-branched aldehydes in weakly basic media with cupric salts as catalyst,* and wish to report that the method is an efficient way to synthesize ketones having one less carbon.

The reaction is highly selective for the aldehyde group, as is illustrated in the following partial synthesis of progesterone. Bubbling air for 16-20 hrs. through a rapidly stirring mixture of 150 g. (0.478 mol.) of 3-oxobisnor-4-cholen-22-al (I), 30 g. (0.268 mol.) of 1,4-diazabicyclo[2.2.2]octane (DABCO) as base, and 3.9 g. of cupric acetate-2,2'-bipyridyl complex (1:1) in 300 ml. of dimethylformamide (DMF) at 40° gave progesterone (II) in 90% yield.** There
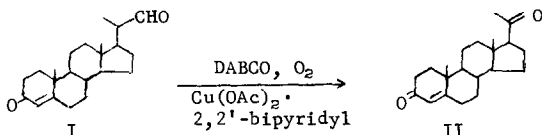
was negligible attack on either the α,β-unsaturated ketone in the A-ring or on the saturated 20-ketone produced during the reaction.

The usefulness of this reaction as a general method for ketone synthesis is shown in Table 1. In each case, the reaction conditions were similar to those described for I except that t-butyl alcohol was used as solvent.

The oxygenation of I to II was investigated in some detail. Both cupric and cuprous salts were found to catalyze oxidative decarbonylation of I, but cupric acetate, preferably complexed with 2,2'-bipyridyl or 1,10-phenantholine, produced II in highest yields. It was important

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*W. Brackman previously used cupric salts to catalyze the oxygenation of β,γ-unsaturated carbonyls to enediones and straight chained aldehydes to acetaldehyde and formic acid. See References 1 and 2.

**All products described in this paper were characterized by comparison with authentic samples, and yields were determined by isolation, with the exception of the acetone (Table 1), which was determined by quantitative vpc.

TABLE 1

Aldehyde	Product	Yield (%) of Ketone
Isobutyraldehyde	Acetone	75
Cyclohexanecarboxaldehyde	Cyclohexanone	66
2-Phenylpropionaldehyde[±]	Acetophenone	78
Diphenylacetaldehyde[±]	Benzophenone	94

[±] These compounds (3) undergo oxygenation in the absence of
cupric ion but at a slower rate.

to choose a basic catalyst that allowed selective deprotonation at a practical reaction rate.
Ordinary tertiary amines such as triethylamine and N,N'-dimethylpiperazine proved much less
satisfactory in this respect than bicyclic amines such as DABCO and 3-quinuclidinol, which have
a sterically unhindered electron pair on nitrogen. The reaction could be conducted in alcohols
(e.g., methanol, t-butyl alcohol) or polar aprotic solvents (e.g., DMF, hexamethylphosphor-
amide), but the former gave lower yields, possibly because of reduced selectivity for position
of deprotonation by the alcoholate in equilibrium with the amine (4).

The oxygenation in DMF at 48° exhibited overall pseudo first-order kinetics (eight deter-
minations over two half-lives) in aldehyde I, but showed first-order dependence on both I and
base DABCO. The reaction rate was independent of oxygen concentration, of cupric ion concentra-
tion, and of the nature and concentration of the complexing ligand. This evidence suggested
that the first and rate-limiting step is enolization of I, catalyzed by DABCO, which is not
consumed by the reaction.

The conversion of I to II resembles the known oxygenation of ketones under strongly enol-
izing conditions (5). Indeed, oxygenation of I without a copper catalyst in potassium t-
butoxide/t-butyl alcohol was recently reported to produce II in 74% yield (6). Under our condi-
tions with DABCO as the basic catalyst, however, no oxygenation occurred in the absence of
cupric ion. That cupric ion functioned as an oxidizing agent was apparent when the reaction was
run with oxygen excluded, causing the blue cupric acetate-2,2'-bipyridyl complex (λ_{max}^{EtOH} 675 mμ)
(7) to be reduced to the corresponding red cuprous complex (λ_{max}^{EtOH} 432 mμ) (7). In the absence
of I, no reduction of cupric ion took place. Since Russell (8) has clearly demonstrated that
carbanions are capable of donating one electron to a suitable acceptor, and Brackman (9) has
shown that cupric ion functions as an acceptor in similar reactions, we visualize a mechanism
(Scheme I) in which the enolate anion (III) is rapidly oxidized by cupric ion to the corres-

ponding enol radical (IV),[±] which on coupling with oxygen leads to the 20-hydroperoxy deriva-

tive (V) of I. The intermediacy of this derivative is strongly indicated by the fact that

SCHEME I
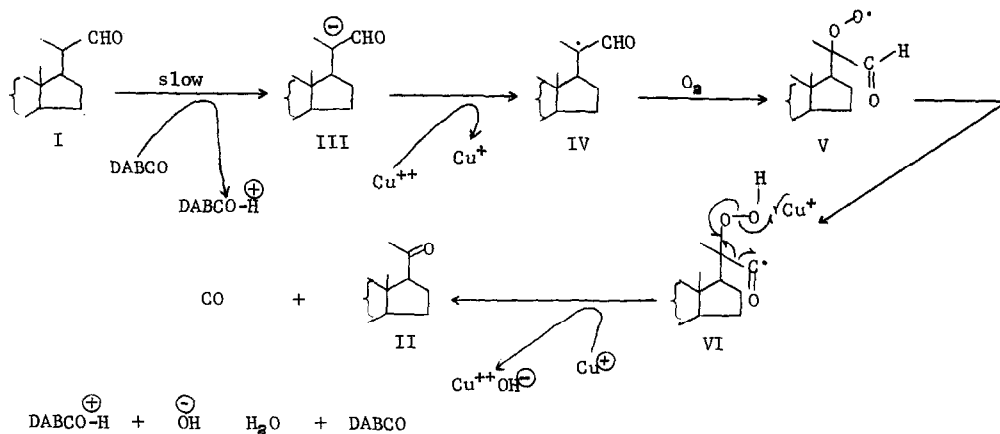
oxygenation of I in the presence of trimethyl phosphite, a reagent which efficiently intercepts

hydroperoxides (10) in the presence of base and oxygen (11), produced in addition to II a 32%

yield of 20-hydroxy-3-ketobisnor-4-cholen-21-al (VII).

Of particular interest is the fact that DABCO was not consumed during oxygenation. It has

been suggested (5) that α-hydroperoxyketones fragment to carboxylic acids and ketones by base-

catalyzed cleavage of perepoxide intermediates such as VIII. If the

oxygenation of I proceeded by this pathway, the C-22 aldehyde carbon
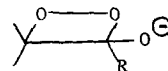
would end up as formic acid, which in turn would neutralize DABCO.   VIII

This possibility was incompatible with our kinetic results and with the fact that DABCO could be

recovered in high yield after oxygenation. Furthermore, a search for formic acid revealed none,

and formic acid was found to be inert under the reaction conditions. The fate of the C-22

aldehyde carbon was indicated by analysis of the effluent gases from the reaction conducted in

both DMF and HMPA. Eighteen mole percent of carbon dioxide was collected as barium carbonate,

and infrared analysis showed that sizable quantities ($\sim 3 \times CO_2$) of carbon monoxide were being

produced. Since cupric ion is known (12) to catalyze oxygenation of carbon monoxide to carbon

dioxide, the carbon monoxide was most likely the initial product.

Karl Fischer determinations showed that one mole of water was produced for each mole of

aldehyde oxidized (13), a result compatible with the above findings. Inhibitors of free radical

[±]In the absence of cupric ion as the electron transfer agent, the oxidation of III to IV
by oxygen must be a relatively slow process (8).

chain reactions, such as 2,6-di-t-butyl-p-cresol, had no effect on either the rate or products
of the oxygenation.

In summary, our evidence points to a mechanism (Scheme I) in which the selective and rate-
limiting enolization of the 22-aldehyde is followed by rapid oxidation (14) of the enolate
anion (III) by one-electron transfer to cupric ion. The resulting enol radical (IV) couples
with molecular oxygen to produce hydroperoxy radical V, which intramolecularly abstracts hydro-
gen from aldehyde to give acyl radical VI. Cuprous ion reduces (15) the hydroperoxide moiety in
VI, resulting in the fragmentation shown in Scheme I to give progesterone (II), carbon monoxide,
and water, and regenerating DABCO and cupric ion. Also compatible with our results is attack
of base on the aldehyde proton of an intermediate α-hydroperoxyaldehyde (formed by cuprous ion
reduction of peroxy radical V and protonation) resulting in heterolytic fragmentation to II,
CO and OH⁻. The low acidity of the aldehyde proton, however, makes this pathway less probable
than the sequence of Scheme I. It seems reasonable that the reactive site of the steroid
molecule remains associated with ionic copper throughout the sequence of Scheme I.

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