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ACID CATALYZED OXIDATION OF ALCOHOLS BY m-CHLOROPERBENZOIC ACID

James A. Cella* and James P. McGrath
Division of Biochemistry
Walter Reed Army Institute of Research
Washington, D.C. 20012

and

Steven L. Regen
Department of Chemistry
Marquette University
Milwaukee, Wisconsin 53233

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Peracids react slowly with alcohols under ordinary conditions[1,2]. Indeed the reaction with alcohols is slow enough to enable peracid mediated conversions of other functional groups in a molecule to be conducted without prior protection of the alcohol[3]. In the presence of catalytic amounts of nitroxide radicals and mineral acids however, secondary alcohols are rapidly and efficiently oxidized to ketones by m-chloroperbenzoic acid (MCPA)[4].

We now report that the oxidation of secondary alcohols to ketones by MCPA occurs readily in THF using HCl as the only catalyst. While this reaction is somewhat less efficient and less general than the nitroxide catalyzed oxidation, it is particularly convenient where applicable and displays a high degree of selectivity (*vide infra*).

The oxidation is accomplished by treating an alcohol, at ambient temperature, with two equivalents of MCPA and a catalytic amount (10 mol%) of HCl in THF for one hour. Table I lists the results of oxidation of a number of representative alcohols by this procedure.

In a representative preparative procedure, a solution of 8.96 g (43.4 mmol) of MCPA (85% Aldrich) in 22 ml of THF (freshly distilled from sodium and benzophenone)[5] is added dropwise to a mixture of 4.0 g (21.7 mmol) of cyclododecanol and 2.17 ml of 1.0 N HCl[6]. After addition of the peracid, the mixture is stirred one hour then diluted with an equal volume of ether and transferred to a separatory funnel. The solution is washed successively with cold 1N NaOH and water. The aqueous extracts are back extracted with ether and the combined organic extracts are dried by passage through a cone of anhydrous Na_2SO_4. Removal of solvent and flash distillation of the residue at reduced pressure affords 3.83 g (97%) of cyclododecanone

TABLE I

ACID CATALYZED OXIDATION OF ALCOHOLS BY m-CHLOROPERBENZOIC ACID[a]

SUBSTRATE	PRODUCT	YIELD (%)[b]
2-octanol	2-octanone	75
2-nonanol	2-nonanone	98
3-hexanol	3-hexanone	92
cyclopropylmethyl carbinol	cyclopropylmethyl ketone	98
cyclododecanol	cyclododecanone	97
cycloheptanol	cycloheptanone	98
cyclohexanol	cyclohexanone	85
4-*tert*-butylcyclohexanol (isomer mixture)	4-*tert*-butylcyclohexanone	75
cyclopentanol	cyclopentanone	67
norborneol	norcamphor	33
borneol	camphor	23
phenyl-2-propanol	phenyl-2-propanone	50

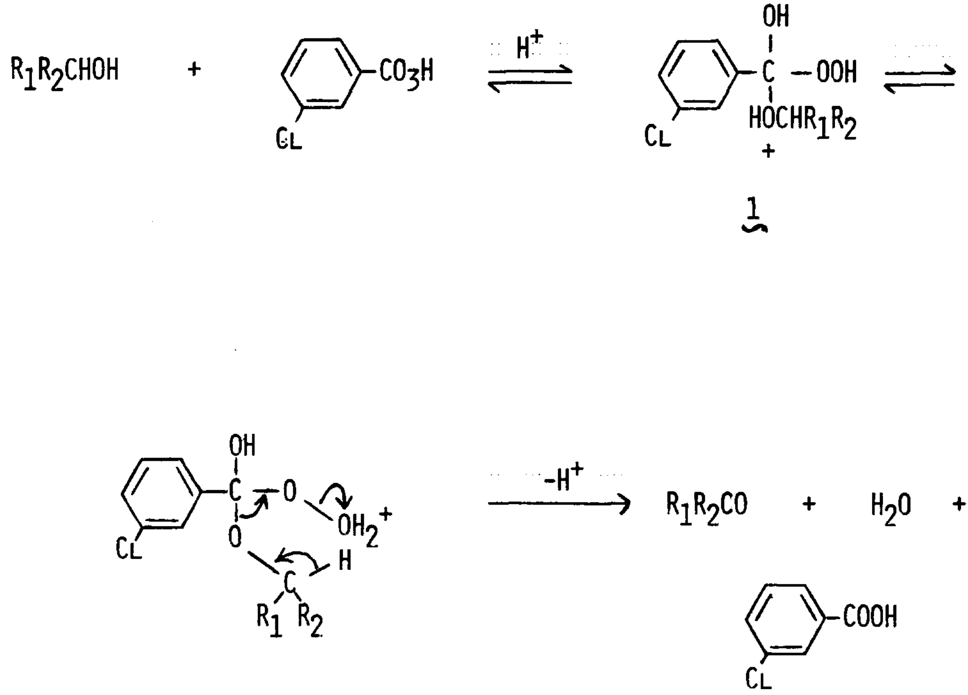
a. Reaction conditions were similar to those described in the text.
b. Yields were determined by vpc.

contaminated with 3-5% of cyclododecanol.

As with the nitroxide catalyzed reaction[4], the oxidation of primary alcohols by this method does not stop at the aldehyde stage. The results in Table I indicate the selective nature of this process. In particular, the reaction works well for sterically unencumbered alcohols (medium, large ring and straight chain) but is significantly less efficient for even slightly hindered alcohols. As an example of the selectivity of this process, oxidation of an equimolar mixture of cycloheptanol and cyclopentanol by this method using an insufficient amount of MCPA afforded cycloheptanone (85%) plus only a small amount (10-15%) of cyclopentanone. In contrast, oxidation of the same alcohol mixture using the nitroxide catalyzed method afforded cyclopentanone as the major (70-80%) product. Clearly the two processes are occuring *via* different mechanisms.

To account for the observed selectivity of this reaction, we propose a mechanism initiated by acid catalyzed addition of the alcohol to the peracid to produce a tetrahedral intermediate, I, which decomposes with loss of a proton to yield a ketone, m-chlorobenzoic acid and water. For those alcohols

SCHEME I



which form the tetrahedral intermediate slowly, a competing side reaction is hydrolysis of the peracid (by water from the catalyst or formed in the reaction). This process destroys peracid and prevents completion of the reaction. Consistent with this hypothesis is the fact that reactions which cease after low conversion can be reinitiated by simply adding more peracid.

A limitation of the present method is the requirement of relatively high acid concentration thus making the reaction unsuitable for the oxidation of acid sensitive compounds. In these cases, the nitroxide catalyzed oxidation, which employs lower acid concentrations, may be applicable. The selective nature of this oxidation reaction suggests application as a method for oxidizing one hydroxyl of a diol whose alcohol functions differ only subtly.

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5. Lower yields were realized when the solvent was not carefully purified.
6. The catalyst can be prepared by bubbling dry HCl into cold THF although aqueous HCl was equally effective and more convenient.