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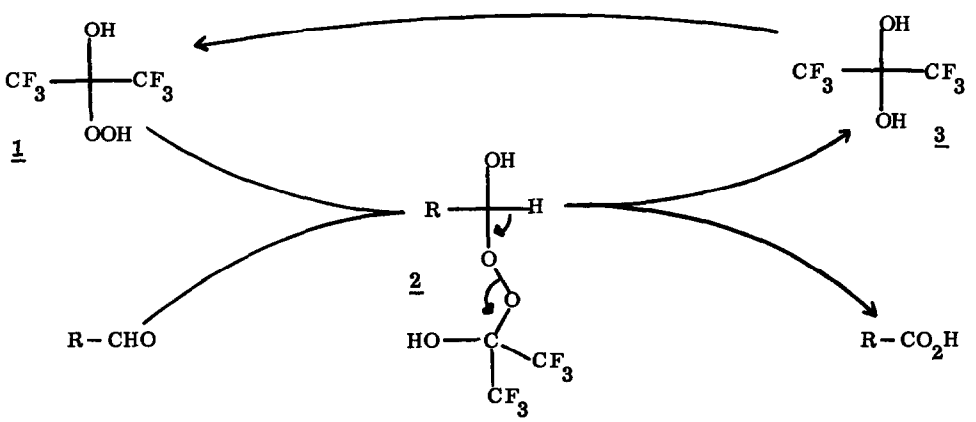
A NEW OXIDATION OF ALDEHYDES TO CARBOXYLIC ACIDS

Bruce Ganem *[1], Richard P. Heggs, Alan J. Biloski and Daniel R. Schwartz

Department of Chemistry
Baker Laboratory
Cornell University
Ithaca, New York 14853

Summary: 2-Hydroperoxyhexafluoro-2-propanol (HPHI) is a selective catalytic and stoichiometric reagent for the oxidation of aldehydes to acids under mildly basic conditions.

The combination of anhydrous CF_3COCF_3 with H_2O_2 produces hydroperoxide 1 (HPHI), a highly regio and stereoselective oxidant for the epoxidation of alkenes.[2] In this Letter we further disclose the synthetic utility of HPHI as a nucleophilic reagent for the conversion of aldehydes to carboxylic acids in the presence of other oxidizable functional groups.[3,4] That 1 might be capable of such transformations was predicated on its resemblance to the bioactive 4a-hydroperoxyflavin coenzymes[5] which, among other natural roles, mediate bacterial chemiluminescence by a similar oxidation of n-tetradecanal to the corresponding fatty acid.[6] The formation of carboxylic acids using HPHI is now thought to occur by the following mechanism[7] and, like epoxidations[8], can be effected with H_2O_2 utilizing catalytic quantities of 1 or 3 in a high-yield, low-cost process.



Consistent with this scheme, the infrared carbonyl absorption of n-heptanal disappears when the aldehyde is mixed with 1 (1 equiv., rt, CH_2Cl_2, 48h), but partitioning with base at this stage affords less than 5% of heptanoic acid 5. Redissolving the residual neutral fraction in CH_3OH-NaOH (reflux) furnishes 5 in 63% yield. Isolation of the suspected peroxy intermediate 2 (R= C_6H_{13}) can be circumvented by performing the reaction at reflux in the presence of suspended Na_2CO_3 and in this fashion heptanal leads directly to 5 in 91% yield. Other results with representative aldehydes are summarized in the Table. With cinnamaldehyde 10, the oxidation to cinnamic acid is complicated by competing Baeyer-Villiger and retro-aldol processes (due to hexafluoroacetone hydrate) which result in phenylacetic acid, benzaldehyde and other uncharacterized products.

A general procedure has been developed utilizing CH_2Cl_2 - Na_2CO_3 along with stoichiometric quantities (1.1-1.5 equiv.) of HPHI (Method A, see Table). If solubility is a problem, the combination of CH_3OH - NaOH (pH 7.5) may alternatively be used although the oxidation is slower in alcohol (Method B). Method B is particularly useful when the selective oxidation of aldehydes in the presence of alkenes is desired (Entry 5). For the large scale synthesis of acids, as little as five mole percent of 1 or 3 can be employed with H_2O_2 as cooxidant in boiling 1,2-dichloroethane. At this temperature, hydrate 3 readily disproportionates with H_2O_2 to form 1.[8]

Some representative experimental procedures follow.

HPHI -- A 250 mL roundbottom flask was fitted with Claisen adapter, pressure-equalizing, graduated addition funnel, Dry Ice condenser and $CaCl_2$ drying tube. Anhydrous CF_3COCF_3 (14 mL, 0.12 mol) was collected by passage through the sidearm of the Claisen tube, then the roundbottom was charged with CH_2Cl_2 (100 mL) and 90% H_2O_2 (3.0 mL, 0.11 mol) and cooled to -60°C. After dropwise addition of HFA, the mixture was warmed to rt and a clear, homogeneous solution resulted which could be titrated (NaI, $Na_2S_2O_3$, ca. 0.7 M) then stored conveniently at 10°C.

OXIDATIONS: Method A -- Anhydrous Na_2CO_3 (1g, 9.5 mmol) was added to a solution of heptanal (0.50g, 4.4 mmol), HPHI (1.15 M in CH_2Cl_2, 6.9 mmol) and CH_2Cl_2 (35 mL) and the mixture brought to reflux for 24h. After cooling, water was added and the layers separated. Acidification of the aqueous phase (5% HCl) and extraction into CH_2Cl_2 furnished heptanoic acid (91%).

Method B -- A solution of powdered NaOH (4.7 mmol) in anhydrous CH_3OH (4.4 mL) was treated with HPHI (4.7 mmol, in CH_3OH or CH_2Cl_2) whereupon the pH fell from 10 to 7.5 and heptanal (3.23 mmol) was added. After 19h at reflux, tlc indicated residual aldehyde consequently more HPHI-NaOH (2 mmol) was added and heating continued another 24h. The bulk of the solvent was then removed in vacuo and the residue partitioned between ether and water. Acidification of the aqueous phase and extraction afforded heptanoic acid in 92% yield.

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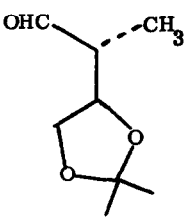
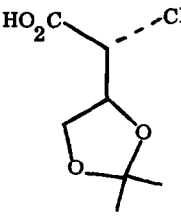
TABLE

Entry	Aldehyde	Method	Products (% Yield)[a,b]
1	heptanal 4	A	heptanoic acid 5 (91)
2	4	B	5 (92)
3	4	catalytic	5 (85)
4	dodecanal 6	A	dodecanoic acid 7 (72) mp 40–42°
5	CH_2=CH$(CH_2)_8$CHO 8	B	CH_2=CH$(CH_2)_8CO_2H$ 9 (75)
6	PhCH=CHCHO 10	A($ClCH_2CH_2Cl$)	$PhCH_2CO_2H$ (35) PhCHO (20)
7	10	B	$PhCH{=}CHCO_2H$ (40)
8	 11[c]	A	 12[c] (30)

(a) Reported yields represent distilled or recrystallized products.

(b) All products were identified by comparison with authentic samples.

(c) Both 11 and 12 were prepared by pyridinium chlorochromate oxidation of the corresponding alcohol; cf W. J. Elliott and J. Fried, J. Org. Chem., 41, 2469 (1976).

REFERENCES AND FOOTNOTES

1. Fellow of the Alfred P. Sloan Foundation, 1978-1980; Recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant, 1978-1983.

2. R. P. Heggs and B. Ganem, J. Amer. Chem. Soc., 101, 2484 (1979).

3. Unlike most chromium and manganese reagents, HPHI does not oxidize alcohols.

4. (a) Argentic oxide (AgO) also oxidizes aldehydes under mild conditions: E. J. Corey, N. W. Gilman, B. Ganem, J. Amer. Chem. Soc., 90, 5616 (1968).
(b) For a good review see J. March, "Advanced Organic Chemistry," 2nd Ed., McGraw-Hill, New York, 1977, pp. 641-643.

5. V. Massey and P. Hemmerich in "The Enzymes," Vol. 12, P. D. Boyer, Ed., Academic Press. New York, 1976, pp. 191-252.

6. S. Ulitzur and J. W. Hastings, Proc. Nat. Acad. Sci. (USA), 76, 265 (1979).

7. This postulate is modeled on the mechanism proposed for flavins: C. Kemal and T. C. Bruice, Proc. Nat. Acad. Sci. (USA), 73, 995 (1976).

8. A large scale, catalytic epoxidation procedure has been submitted to Organic Syntheses; preprints are available.

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