Oxidation of Methyl Trimethylsilyl Ketene Acetals to α-Hydroxyesters with Urea Hydrogen Peroxide Catalyzed by Methyltrioxorhenium

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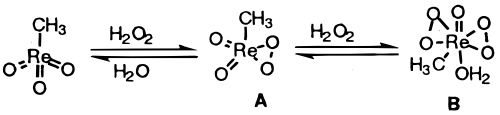
In the presence of catalytic amounts of MTO, methyltrioxorhenium, methyl trimethylsilyl ketene acetals are oxidized with urea hydrogen peroxide to afford α-hydroxy and α-siloxy esters. On treatment with potassium fluoride, the α-hydroxy esters are obtained in high yields.

Introduction

Lead(IV) carboxylates,[1] hypervalent iodine,[2] *m*-chloroperbenzoic acid (*m*-CPBA),[3] and dimethyldioxirane (DMDO)[4] can be used to oxidize esters via their ketene acetals to α-hydroxy carbonyl compounds. Catalytic reagents are Mn^{II}(salen) complexes with various oxidants[5] and cobalt[6] or nickel(II)[7] complexes with oxygen. Few reports of hydrogen peroxide as the oxidant have appeared,[8] presumably owing to the hydrolytic instability of ketene acetals. The α-hydroxy esters are synthetic intermediates of widespread use through the independent manipulation of the hydroxy and ester groups. For example, they are used in the preparation of esters and acids functionalized at the 2-position, like 2-oxo esters and acids.[9] α-Hydroxy esters are also used in the synthesis of certain natural products.[10] We are unaware of any major application that relies on the presence of the two functional groups; the uses are those of the independent alcohol and ester groups.

Methyltrioxorhenium (CH_3ReO_3, abbreviated as MTO) is a well-established catalyst for the reactions of hydrogen peroxide,[1,11] including the epoxidation of alkenes.[12−15] The active forms of the catalyst are the monoperoxo and diperoxo complexes formed in reversible equilibria, eq 1.



(1)

Water-labile silyl enol ethers form α-hydroxy ketones with aqueous hydrogen peroxide and the MTO catalyst in acetonitrile.[16] We sought to extend this methodology to ketene acetals, which are even more hydrolytically sensitive owing to the presence of an additional alkoxy functionality,[17,18] because peroxide is such a convenient laboratory reagent. For our study, we selected methyltrimethylsilyl ketene acetals. Herein, we report the effectiveness of an optimized procedure that relies upon the anhydrous material urea−hydrogen peroxide, UHP, and quite importantly, the presence of pyridine.

Experimental Section

Reagents. The ketene acetals were prepared from the parent esters and trimethylsilyl chloride using a published procedure.[19] The esters were purchased and used as such except for methyl 2-phenylpropanoate, which was obtained from 2-phenylpropanoic acid (10 g, 67 mmol) upon refluxing for 7 days in methanol (50 mL in the presence of catalytic amount of *p*-toluenesulfonic acid (0.6 g, 3.3 mmol). After completion, the reaction mixture was dissolved in ether, washed with saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Solvent evaporation followed by distillation afforded 8.64 g of methyl 2-phenylpropanoate.

Oxidation of Ketene Acetals. The ketene acetal (2.5 mmol) was introduced dropwise over 5 min into a cooled mixture (0 °C) of UHP (0.35 g, 3.75 mmol), pyridine (0.05 g, 0.625 mmol), and MTO (0.031 g, 0.125 mmol) in 99:1 acetonitrile/acetic acid (5 mL). After being stirred for an additional 5 min at room temperature, the reaction mixture was treated with a minimal amount of saturated sodium bicarbonate solution to neutralize acetic acid and destroy the catalyst. The mixture was then dissolved in dichloromethane and the organic layer separated and dried. After filtration and solvent

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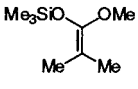
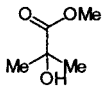
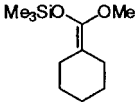
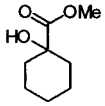
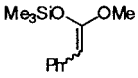
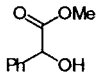
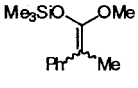
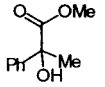
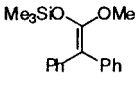
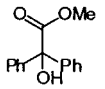
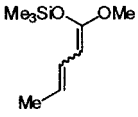
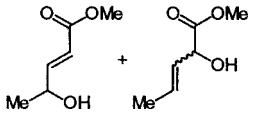
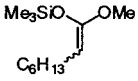
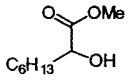
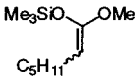
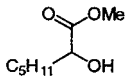
Table 1. Catalytic Preparation of α-Hydroxy Esters

Entry	Substrate	Product	% Yield [a,b]
1			>95 (71)
2			>95 (77)
3 [c]			>95 (81)
4 [d]			>95 (85)
5			94 (75)
6 [d]			>95 (70) [e,f]
7 [g]			50
8 [h]			45

[a] NMR yield based on the ratio of methyl ester peak intensities of the α-hydroxy and of α-siloxy esters versus the methyl peak intensity of the parent ester. [b] Isolated yield after desilylation, in parentheses. [c] A 70:30 mixture of isomers by NMR. [d] A 60:40 mixture of isomers by NMR. [e] Product ratio 80:20 by NMR. [f] Combined yield of both products. [g] A mixture of isomers 70:30 by NMR. [h] A mixture of isomers 70:30 by NMR.

removal, the crude product was dissolved in a saturated solution of potassium fluoride in methanol and stirred for 1 h. The solution was then dissolved in water and extracted with dichloromethane. After drying over anhydrous sodium sulfate and solvent removal, the product was purified by flash chromatography on silica gel (pentane/acetone)

Results

The experimental procedure developed for the oxidation of silyl enol ethers with aqueous hydrogen peroxide in acetonitrile in the presence of pyridine[20] turned out to be inadequate for the more hydrolytically labile ketene acetals. Initial experiments with 1-methoxy-1-trimethylsiloxy-1-methylenecyclohexane, using the same procedure, showed significant substrate hydrolysis (70%). We found, however, upon replacing aqueous hydrogen peroxide with UHP, a convenient and inexpensive source of anhydrous hydrogen peroxide, that hydrolysis decreased to about 30%. Use of a lower temperature, 0 °C, and dropwise addition of the substrate, afforded nearly complete oxidation. We applied this procedure to a number of different ketene acetals. The results are shown in Table 1.

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Table 2. Effect of Pyridine on the Oxidation of (1-Methoxyheptenyloxy)trimethylsilane

entry	additive	% yield[a]
1	4-methylpyridine	60
2	4-methoxypyridine	70
3[b]	pyridine	35
4[b]	4-methylpyridine	55
5[b]	4-methoxypyridine	65
6[c]	pyridine/2,6-dimethylpyridine	75
7[c]	pyridine/2, 4, 6-trimethylpyridine	81
8[c]	pyridine/4-methyl-2.6-di-*tert*-butylpyridine	56
9	4-methyl-2.6-dimethylpyridine	<10[d]

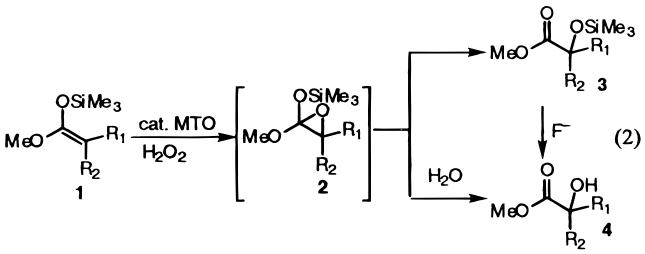
[a] NMR yield based on the ratio of methyl ester peak intensities of the of α-hydroxy esters and of α-siloxy esters versus the parent ester. [b] No acetic acid present. [c] 1:1 ratio with the concentration of pyridine equal in all experiments. [d] Determined by GC/MS.

Ketene acetals with two β-alkyl substituents, or >1 unsaturated substituent, underwent oxidation cleanly. One conjugated substrate has a double bond (entry 6), such that two possible modes of oxygen addition will yield two products. The addition of oxygen at the ketene acetal double bond predominates, yielding the nonconjugated product. The rationale for this preference might be the coordination of the rhenium catalyst to an oxygen atom of the ketene acetal moiety.

The two substrates having only one β-substituent were predominantly hydrolyzed. To improve the extent of oxidation for these substrates, further optimization was undertaken. Pyridine was replaced by the more basic 4-substituted pyridines; there was an improvement, but it was insufficient. Exclusion of acetic acid had a small deleterious effect (entries 4−6). The best results were obtained with a reaction system containing both pyridine and a bulky pyridine (Table 2, entries 6 and 7), although a bulky pyridine itself fails (Table 2, entry 9).

Discussion

The Effect of Structure. The oxidation of ketene acetals, as in the case of enol ethers, presumably proceeds via an unstable transient epoxide **2** that undergoes either silyl migration or hydrolysis to afford the α-siloxy ester **3** or the α-hydroxy methyl ester **4**.[16] Subsequent hydrolysis of the α-siloxy ester is slow under the employed conditions, and fluoride treatment was needed to effect desilylation, eq 2.



(2)

The outcome of the oxidation reactions appears to be the result of a balance between the rates of protonation of ketene acetals and oxygen transfer. The hydrolysis of ketene acetals is known to proceed through rate-determining irreversible protonation followed by hydrolysis of the resulting oxocarbocation to the parent carboxylic ester:[1,21,22]

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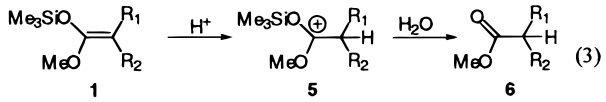
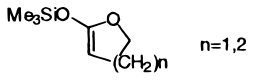


(3)

It has been shown that the rate of protonation of simple enol ethers depends on the extent of substitution at the β-carbon.[23] The more substituted enol ethers are less prone to protonation. Ground-state stabilization has been invoked to rationalize this trend. The same trend might be operable in the case of ketene acetals. Nevertheless, more substituted ketene acetals are, like olefins, expected to react faster with the peroxo adducts due to the increased electron density in the ketene acetal double bond. The presence of unsaturated substituents in the β-position should decrease the rates of both processes. Apparently the effect is more pronounced on the rate of protonation leading to oxidation in preference to hydrolysis, even with only one β-substituent. Our attempts to effect the oxidation of ketene acetals derived from 5- and 6-membered cyclic lactones failed, yielding only the parent lactones. This is not surprising since their propensity for protonation has been well documented. For example, with *m*-CPBA they undergo exclusive protonation rather than oxidation.[3]



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The Role of Pyridine. Pyridine, when introduced to the reaction system, can prevent the hydrolysis of epoxides formed during the epoxidation of olefins with hydrogen peroxide catalyzed by MTO. This significantly improved the effectiveness of the catalyst and broadened its applicability.[24,25] Pyridine plays at least two roles in the MTO-peroxide system,[25] as a Lewis base to coordinate to MTO, thereby accelerating the rate of peroxorhenium formation, and as a Brønsted base. It lowers the acidity of the medium, helping to lessen the rate at which acid-sensitive reagents (here, ketene acetals) and products (epoxides) are lost. Pyridine coordinates to MTO, strongly accelerating the rate of the peroxide binding steps, eq 1.[25] This shortens the time that the peroxorhenium catalyst must last before deactivation.[26] The reaction time is particularly important in this heterogeneous system, because without pyridine the reaction between UHP and MTO is very sluggish. A low concentration of pyridine proved inadequate,[24] even worse than its omission, leading only to the base-catalyzed decomposition of catalyst.[26,27] For the same reason, pyridines with bulky substituents in positions 2 and 6, used alone, do not show a stabilizing effect.

It is known that MTO is deactivated by conversion to perrhenic acid.[26] An obvious role for pyridine is therefore to act as a buffer by neutralizing the perrhenic acid formed by the decomposition of the catalyst. This leaves pyridinium cations as well as acetic acid as the principal acidic species responsible for the protonation of ketene acetals. Acetic acid favors this reaction because it buffers the pyridine/pyridinium system. Relevant pK_a values of pyridinium ions in aqueous solutions are:[28,29] Py, 5.25; 4-MePyH$^+$, 6.02; 4-MeOPyH$^+$, 6.47; 2,6-Me$_2$PyH$^+$, 6.75; and 2,4,6-Me$_3$PyH$^+$, 7.43. This leaves sufficient pyridine for the beneficial effect of its coordination, while not making the system too basic that MTO and its peroxides are rapidly destroyed. Pyridinium cations, being less acidic than HOAc, will be poorer reagents for substrate hydrolysis.

The best results were obtained with the most basic bulky pyridines used in conjunction with pyridine. The steric bulk around the pyridine nitrogen presumably also plays a role as the most sterically protected 4-methyl-2,6-di-*tert*-butylpyridine gives results slightly better than pyridine itself, even though it is less basic than pyridine.[30−32] This simple explanation, however, does not suffice: 2,6-dimethylpyridine by itself performs worse even though it is more basic than pyridine itself. A possible explanation might be that even though the bulky pyridine can effectively neutralize the perrhenic acid it is unable to coordinate to MTO and the peroxo adducts **A** and **B**.

It is known that **B** coordinates one molecule of water[13] and therefore represents a Brønsted acid; its pK_a is 3.8.[13] Similar binding of water molecules, also be possible for monoperoxo adduct, could not be detected by ^{1}H NMR.[26] The role of sterically unhindered pyridines hence might be to neutralize the acidity of the peroxo adducts by displacing the coordinated water molecules. However, no direct evidence supports that, and it has been established that pyridine binds only to MTO, not to **A** and **B**.[25]

Acknowledgment. This research was supported by the U. S. Department of Energy, Office of Basic Energy Sciences, Division of Chemical Sciences under contract W-7405-Eng-82.

Supporting Information Available: NMR data for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000212E

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