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Novel applications of the methyltrioxorhenium/hydrogen peroxide catalytic system

by

Sasa Zivorad Stankovic

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of
DOCTOR OF PHILOSOPHY

Major: Organic Chemistry
Major Professor: James H. Espenson

Iowa State University
Ames, Iowa
2000

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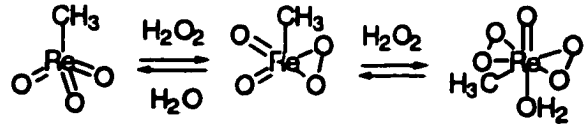
GENERAL INTRODUCTION

Introduction

Methylrhenium trioxide (MTO), CH_3ReO_3, was first prepared in 1979.[1] An improved synthetic route to MTO was devised from dirhenium heptoxide and tetramethyltin in the presence of hexafluoro glutaric anhydride was reported by Herrmann in 1992.[2]

In spite of its early discovery its potential as a catalyst was recognized in 1991 by Herrmann and co-workers.

The most important property of MTO is its ability to react with hydrogen peroxide in reversible equilibria to form two peroxo adducts, **A** and **B**, respectively (eq. 1). MTO/hydrogen peroxide catalytic system has been shown to oxidize alkenes,[3-5] alkynes,[6] various nitrogen compounds,[7-11] sulfides,[12] and phosphines.[13] The peroxo adducts are themselves able to transfer oxygen to a number of nucleophilic substrates as shown in scheme 1.



A **B** (1)

This renders MTO an attractive "green" catalyst. It possesses other desirable properties, like solubility in water and many organic solvents, stability towards high concentrations of acids (pH 0-3) and stability in air.

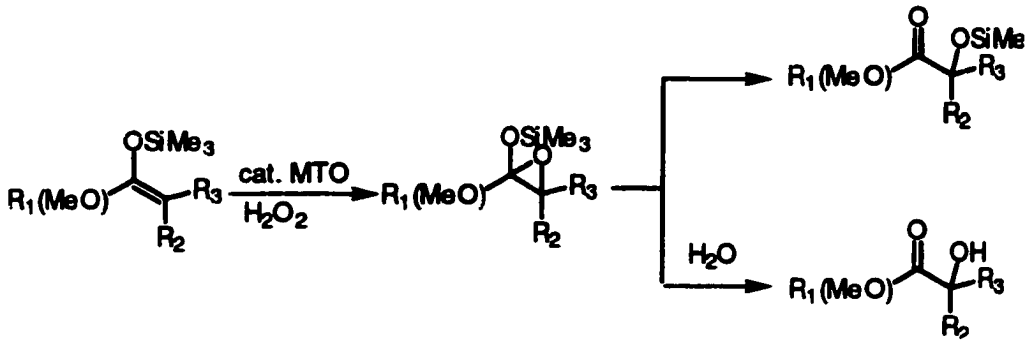
Hydrogen peroxide thus far remains the only oxidant that can react with MTO, nevertheless it can be applied either as aqueous solution or in one of the anhydrous forms (urea hydrogen peroxide addition compound or bis(trimethylsilylperoxide).

A significant breakthrough in the chemistry of MTO was achieved when it was realized that pyridine, if present in a certain window of concentration, can neutralize the acidity of the catalyst and enhance the selectivity of the epoxide formation in olefin epoxidation reactions.[14] Furthermore pyridine exhibits other desirable properties, namely it increases the rate of formation of the peroxo adducts, which becomes very important especially with substrates of high reactivity where the peroxo adduct formation cannot compete with the rate of substrate oxidation. By increasing the rate of formation of the bisperoxo adduct **B**, it also stabilizes the catalyst by transferring it to this stable form. Pyridine was also found to increase the rate of oxygen transfer to the substrate.[15]

During the course of research on this dissertation we uncovered other reactions where the presence or absence of pyridine can, in some cases dramatically, affect the reaction outcome. The most striking examples thus far found are those of silyl enol ethers and ketene acetals. The main structural feature of these compounds is the presence of an activated electron rich double bond due to the presence of one or two

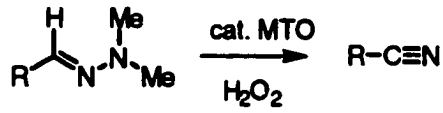
electron donating siloxy or alcoxy groups in silyl enol ethers and ketene acetals, respectively. Owing to the presence of such electron donating groups these substrates present ideal targets for an electrophilic catalyst like MTO. However, their oxidation fails entirely if the catalyst is used in a conventional manner without any pyridine additives and the only products are the parent carbonyl compounds (ketenes and esters). In the presence of pyridine, these reactive substrates are oxidized to a mixture of α-hydroxy and α-siloxy carbonyl compounds (eq. 2). For the oxidation of these compounds, we developed procedures with acetic acid used alongside pyridine since such combination increases the stability of the catalyst and improves the selectivity. While silyl enol ethers can be oxidized using aqueous hydrogen peroxide in acetonitrile, for the more reactive ketene acetals the use of anhydrous urea-hydrogen peroxide addition compound, an anhydrous form of hydrogen peroxide, was required. Both methods represent the first successful application of hydrogen peroxide for the oxidation of these water labile compounds.

Another reaction that exhibits the effect of pyridine, albeit less dramatically, is the oxidation of N,N-dimethylhydrazones derived from aldehydes to the corresponding nitriles (eq. 3). Here, in the absence of pyridine the oxidation to nitriles is accompanied to some extent by hydrolysis to the parent aldehydes.



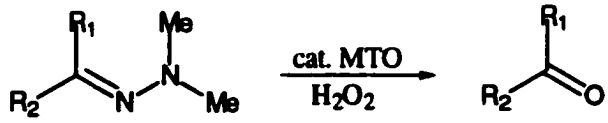
(2)

However if pyridine is present, the oxidation to the nitriles is essentially complete. The use of pyridine allows the use of a rapid procedure. Other techniques can also be applied, for example cooling the reaction mixture stabilizes the catalyst and reduces the extent of hydrolysis.



(3)

In addition to aldehyde N, N-dimethylhydrazones, the analogous compounds derived from ketones also undergo oxidation to yield the parent ketones. This reaction is also described in this thesis and its mechanism studied in some detail (eq. 4).



(4)

Dissertation Organization

This dissertation consists of four chapters. The first two chapters deal with the oxidation of water sensitive olefinic compounds with the

hydrogen peroxide/MTO system. Chapters III and IV focus on the oxidation of hydrazones with the same catalytic system. Chapter I has been published in *The Journal of Organic Chemistry and* Chapter III in *Chemical Communications.* Chapters II and IV have been submitted for publication in *The Journal of Organic Chemistry.* Each section is self-contained with its own equations, tables, figures and references. All of the work in this dissertation was performed by this author.

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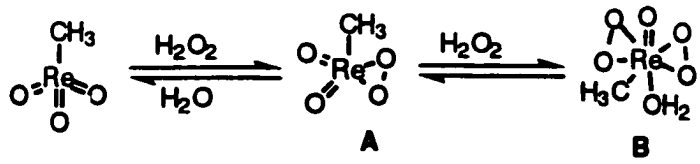
CHAPTER I. FACILE OXIDATION OF SILYL ENOL ETHERS WITH HYDROGEN PEROXIDE CATALYZED BY METHYLTRIOXORHENIUM

A note published in *The Journal of Organic Chemistry*

Saša Stanković and James H. Espenson

In the presence of catalytic amounts of MTO, silyl enol ethers are oxidized with hydrogen peroxide to afford α-hydroxy and α-siloxy ketones. On treatment of the mixture with potassium fluoride, the former are obtained in high yields.

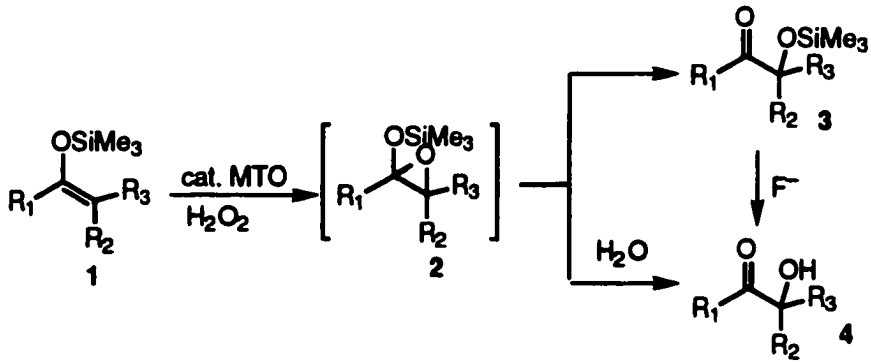
Methyltrioxorhenium (CH_3ReO_3, abbreviated as MTO) is a well-established catalyst for the reactions of hydrogen peroxide,[1,2] including the epoxidation of alkenes.[3-6] The active forms of the catalyst are the monoperoxo and diperoxo complexes formed in reversible equilibria, eq. (1):



(1)

We have devised a convenient and efficient method for preparing α-hydroxy ketones from silyl enol ethers with H_2O_2 as the oxidizing agent and MTO as the catalyst in acetonitrile. The silyl enol ethers **1** were

converted to the α-hydroxy ketones **4**, accompanied by the corresponding α-hydroxy siloxy ketones **3**, presumably through the epoxide **2**, which partitions by hydrolysis to **4** or silyl rearrangement to **3**, eq. 2.[7-9] Successive disilylation of the crude reaction mixtures afforded **4** in high yields. The compounds are presented in **Table 1**.



(2)

This conversion was best carried out in acetonitrile solutions containing pyridine and acetic acid. The ethers **1** are moisture-sensitive compounds, especially when acids or bases are present. Indeed, our initial attempts with H_2O_2/MTO but lacking pyridine and acetic acid failed, giving only hydrolysis to ketones; apparently MTO or **A** or **B** are strong enough Lewis acids to catalyze hydrolysis. Recently, it has been shown that pyridine is able to suppress the Lewis acidity of MTO and its peroxo adducts and prevent the hydrolysis of epoxides formed by the oxidation of alkenes with hydrogen peroxide/MTO system.[10] Also, pyridine accelerates peroxo complex formation as in eq. 1. The use of pyridine

alone is not satisfactory, since MTO is concurrently deactivated by conversion to perrhenate.[11] To stabilize the catalyst and to allow higher levels of the enol ether, and lower catalyst concentrations, acetic acid was added along with pyridine as a component of the solvent mixture. With 5% HOAc, 0.2 mol% MTO sufficed, with little or no hydrolysis of the ether. Pyridine is necessary, however, as HOAc alone gives only total hydrolysis. This system constitutes a buffer, with each component having a separate role. Pyridine reduces the Lewis acidity of the catalyst, thus preventing the hydrolysis of **1**; HOAc lowers the basicity of the solution, prolonging the catalyst's lifetime. The ratio HOAc/Py was ~9:1.

As shown in eq. 2, an amount of **3** accompanies the desired product in an amount depending on the substrate. These materials were not isolated, but were observed in the GC–MS. Under the experimental conditions, slow hydrolysis of **3** to **4** was found when the potassium fluoride workup was delayed.

The method works efficiently when **1** does not have an electron-withdrawing group conjugated with the enol ether double bond. In the case of 1-phenyl-1-trimethylsiloxyethene (entry 8), the yield is only 60%, presumably due to its lower reactivity toward oxidation, allowing hydrolysis to compete. The even less reactive 4-trimethylsiloxy-3-penten-2-one gave hydrolysis only, resulting in 2,4-pentanedione.

The literature reports such reactions, utilizing reagents like peracids,[7-9] chromyl chloride,[12] hypervalent iodine,[13] dimethyldioxirane,[14] sulfonyloxaziridines,[15] osmium tetroxide,[16] triphenyl phosphite ozonide,[17] lead tetrabenzoate,[18] and molecular oxygen.[19] Optically active α-hydroxy carbonyl compounds have been prepared from silyl enol ethers using a number of oxidants with (salen)Mn(III) complex as a catalyst.[20] The method described here has the advantage over most of the mentioned methods because aqueous hydrogen peroxide, a cheap and readily available oxidizing agent, was used; also MTO is commercially available and the procedure gives high yields in reasonable reaction times. Recently, a moderately successful oxidation of silyl enol ethers with aqueous hydrogen peroxide catalyzed by peroxotungstophosphate has been reported.[21]

The experimental protocol is this: **1** (0.10 mmol) was added to a rapidly-stirred solution of MTO (0.2 mM), hydrogen peroxide (0.2 M, added as a 30% solution in water), pyridine (0.1 M) in 1.0 mL of acetonitrile/HOAc, 95:5 by volume. After 15 min., most of the acetonitrile was removed by rotary evaporation, and the residue poured into 5 mL of satd. KF in methanol. Stirring was continued for 2 hr, the solution dissolved in ether, and washed first with satd. sodium bicarbonate and then water. The ether layer was dried, and the product obtained by

evaporation after column chromatography (n-hexane/acetone). This procedure was successfully scaled up by a factor of 100 to obtain the isolated yields reported in the table.

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research. Some of this research was conducted in facilities of the Ames Laboratory, operated for the U. S. Department of Energy under contract W-7405-Eng-82.

Table 1. Synthesis of α-hydroxy carbonyl compounds

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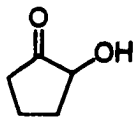
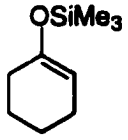
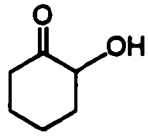
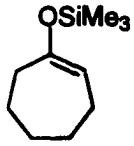
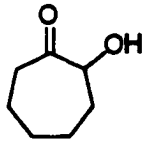
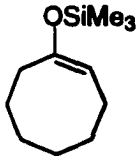
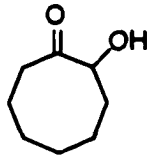
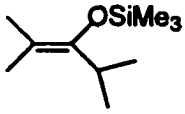
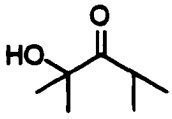
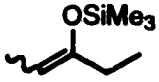
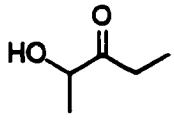
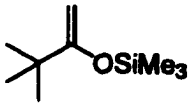
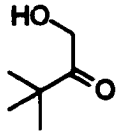
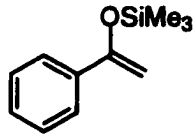
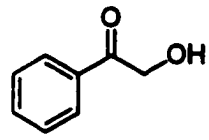
1			96
2			97 (90)[b]
3			99 (91)[b]
4			99
5			95
6[c]			99
7			100

Table 1. (continued)

Entry	Trimethylsilyl enol ether	Product	Yield [a]
8			60

a) Combined GC/MS yields of both α-hydroxy and α-siloxy ketones, the balance being the corresponding ketone formed by the hydrolysis of the starting trimethylsilyl enol ether. In two cases, entries 2 and 3, the GC/MS yield was confirmed from the amount of the nonoxidized ketone, which was determined by the method of standard addition.

b) Isolated yield from a reaction on a scale of ~2 g.

c) Mixture of isomers, trans/cis 97:3 from GC–MS.

Supporting Information

^{1}H and ^{13}C NMR data for the different hydroxy ketones

Product	^{1}H NMR: δ/ppm	^{13}C NMR: δ/ppm
2-hydroxycyclopentanone	4.04 (m, 1H), 1.80-2,40 (m, 6H),	218.40, 75.67, 33.92, 30.59, 16.27
2-hydroxycyclohexanone	4.07 (dd, 1H) 1.35-2.55 (m, 8H)	211.36, 75.26, 39.42, 36.63, 27.48, 23.29
2-hydroxycycloheptanone	4.25 (dd, 1H) 1.20-2.75 (m, 10H)	213.84, 77.04, 40.08, 33.77, 29.53, 26.63, 23.45
2-hydroxycyclooctanone	4.15 (dd, 1H) 0.80-2.80 (m, 12H)	217.46, 76.14, 37.21, 29.23, 28.57, 25.43, 24.42, 22.05
2,4-dimethyl-2-hydroxy-3-pentanone	3.05 (septet, 1H) 1.38 (s, 6H) 1.10 (d, 6H)	218.74, 76.46, 33.79, 26.05, 19.79
2-hydroxy-3-pentanone	4.24 (q, 1H) 2.50 (m, 2H) 1.37 (d, 3H) 1.11 (t, 3H)	213.03, 72.37, 30.72, 19.92, 7.56
3,3-dimethyl-1-hydroxy-2-butanone	4.37 (s, 2H) 1.17 (s, 9H)	215.19, 63.85, 42.05, 26.21

2-hydroxyacetophenone	7.40-7.65 (m, 3H) 7.85-7.95 (m, 2H) 4.86 (s, 2H)	198.38, 134.25, 133.40, 128.92, 127.64, 65.38

CHAPTER II. OXIDATION OF METHYL TRIMETHYLSILYL KETENE ACETALS TO α-HYDROXYESTERS WITH UREA HYDROGEN PEROXIDE CATALYZED BY METHYLTRIOXORHENIUM

A paper submitted to *The Journal of Organic Chemistry*

Saša Stanković and James H. Espenson

Abstract

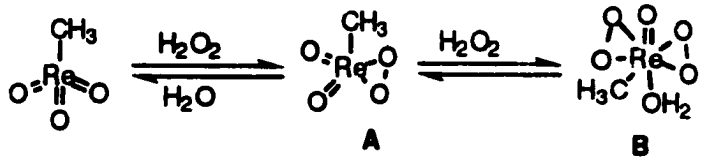
In the presence of catalytic amounts of MTO, methyltrioxorhenium, methyl trimethylsilyl ketene acetals are oxidized with urea hydrogen peroxide to afford α-hydroxy and α-siloxy esters. On treatment with potassium fluoride, the α-hydroxy esters are obtained in high yields.

Introduction

Lead(IV) carboxylates,[1] hypervalent iodine,[2] meta-chloroperbenzoic acid (MCPBA)[3] and dimethyldioxirane (DMDO)[4] can be used to oxidize esters *via* their ketene acetals to α-hydroxy carbonyl compounds. Catalytic reagents are manganese^{III}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.

Methyltrioxorhenium (CH_3ReO_3, abbreviated as MTO) is a well-established catalyst for the reactions of hydrogen peroxide,[1,9] including the epoxidation of alkenes.[10-13] 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 MTO catalyst in acetonitrile.[14] We sought to extend this methodology to ketene acetals, even more hydrolytically sensitive owing to the presence of an additional alcoxy functionality,[15,16] because peroxide is such a convenient laboratory reagent. For our study we selected methyl trimethylsilyl ketene acetals. Herein we report the effectiveness of an optimized procedure that relies upon the anhydrous material urea-hydrogen peroxide, UHP.

Experimental section

Reagents. The ketene acetals were prepared from the parent esters and trimethylsilyl chloride using a published procedure.[17] 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 seven 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 (52.7 mmol) of methyl 2-phenylpropanoate.

Oxidation of ketene acetals. The ketene acetal was introduced dropwise over five 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). The reaction mixture was then stirred for an additional five min at room temperature. After filtration and solvent removal, the crude reaction mixture was dissolved in saturated solution of potassium fluoride in methanol and stirred for one hour. 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 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**.

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.

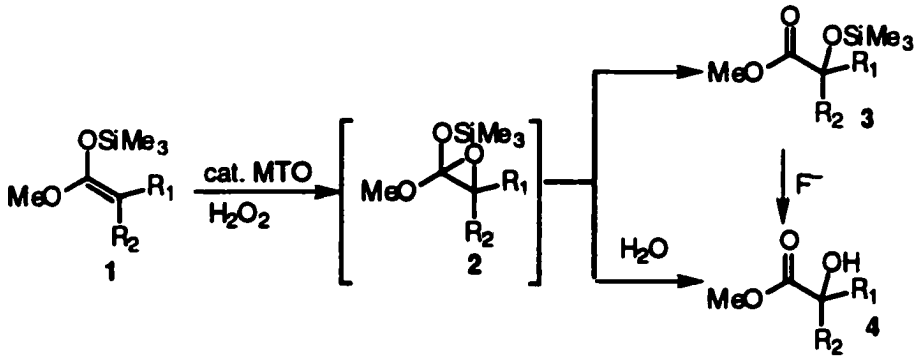
The two substrates having only one β-substituent were predominantly hydrolyzed. To improve the extent of oxidation for these substrates, further optimization was undertaken. Pyridine was replaced by the more basic 4-substituted pyridines; there was an improvement, but it was insufficient. Exclusion of acetic acid had a small deleterious effect (entries 4, 5 and 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

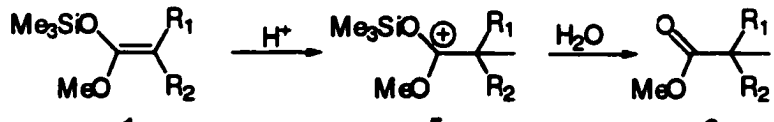
The effect of structure. The oxidation of ketene acetals, as in the case of enol ethers, presumably proceeds via an unstable transient epoxide **2** which undergoes either silyl migration or hydrolysis to afford the α-siloxy ester **3** or the α-hydroxy methyl ester **4**.[14] Subsequent hydrolysis of the α-siloxy ester is slow under the employed conditions, and fluoride treatment was needed to effect desilylation, eq. 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:[1,18,19]



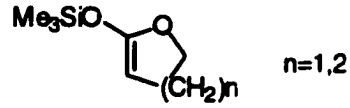
(2)



(3)

It has been shown that the rate of protonation of simple enol ethers depends on the extent of substitution at the β-carbon.[20] 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 MCPBA they undergo exclusive protonation rather than oxidation.[3]



6

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.[21,22] Pyridine plays at least two roles in the MTO-peroxide system,[22] 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.[22] This shortens the time that the peroxorhenium catalyst must last before deactivation.[23] 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,[21] even worse than its omission, leading only to the base-catalyzed decomposition of catalyst.[23,24] 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.[23] 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:[25,26] PyH, 5.25; 4-MePyH$^+$, 6.02; 4-MeOPyH$^+$, 6.47; 2,6-Me_2PyH$^+$, 6.75; and 2,4,6-Me_3PyH$^+$, 7.43. This leaves sufficient pyridine for the beneficial effect of its coordination, while not making the system to 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-t-butylpyridine gives results slightly better than pyridine itself, even though it is less basic than pyridine.[27-29] 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 too coordinate to MTO and the peroxo adducts **A** and **B**.

It is known that **B** coordinates one molecule of water[11] and therefore represents a Brønsted acid; its pK_a is 3.8.[11] Similar binding of water molecules, also be possible for monoperoxo adduct, could not be detected by ^{1}H-NMR.[23] 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**.[22]

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Acknowledgment

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Table 1. Catalytic Preparation of α-Hydroxy Esters

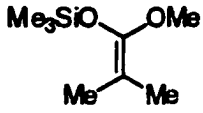
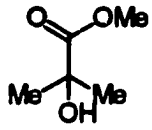
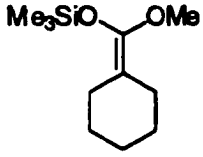
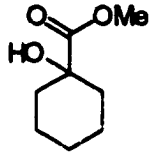
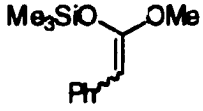
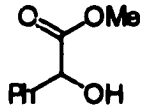
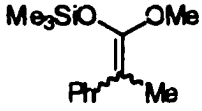
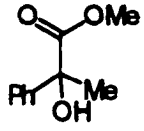
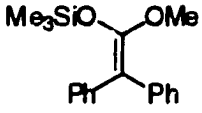
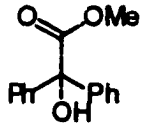
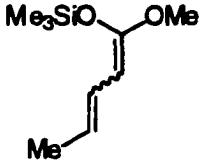
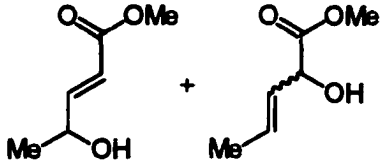
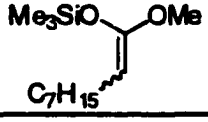
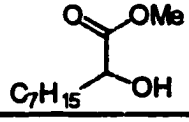
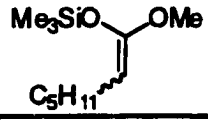
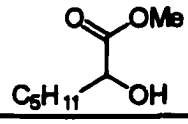
Entry	Substrate	Product	% Yield [a,b]
1			>95 (71)
2			>95 (77)
3 [c]			>95 (81)
4 [d]			>95 (85)
5			94 (75)
6 [d]			>95 (70) [e,f]
7 [g]			50

Table 1. (continued)

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.

Table 2. The 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

Supporting information

^{1}H and ^{13}C NMR data for methyl 2-phenylpropanoate (in $CDCl_3$ with respect to Me_4Si, 400 MHz)

^{1}H: 7.33-7.22 (m, 5H), 3.71 (q, J=7.1 Hz, 1H), 3.64 (s, 3H), 1.49 (d, J=7.1 Hz, 3H)

^{13}C: 174.96, 140.50, 128.59, 127.41, 127.09, 51.97, 45.36, 18.55

^{1}H and ^{13}C NMR data for the ketene acetals (in $CDCl_3$ with respect to Me_4Si, 400 MHz)

(1-methoxy-2-methylprop-1-enyloxy)trimethylsilane

^{1}H: 3.47 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H) 0.17 (s, 9H)

^{13}C: 149.35, 90.93, 56.54, 16.87, 16.13, 0.03

1-methoxy-1-trimethylsiloxymethylenecyclohexane

^{1}H: 3.39 (s, 3H), 2.09 (m, 2H), 2.01 (m, 2H), 1.44 (m, 6H), 0.19 (s, 9H)

^{13}C: 147.10, 99.36, 56.90, 27.70, 27.26, 27.04, 26.77, 26.60, -0.10

(1-methoxy-2-phenylethenyloxy)trimethylsilane two isomers E/Z 70:30% as determined by NMR

E isomer: ^{1}H: 7.42-7.52 (m, 2H), 7.26-7.31 (m, 2H), 7.05-7.10 (m, 1H), 4.73 (s, 1H), 3.74 (s, 3H), 0.38 (s, 9H);

^{13}C: 154.77, 136.68, 128.07, 126.46, 123.72, 85.74, 53.74, –0.20

Z isomer: ^{1}H: 7.42-7.52 (m, 2H), 7.26-7.31 (m, 2H), 7.05-7.10 (m, 1H), 4.65 (s, 1H), 3.72 (s, 3H), 0.34 (s, 9H)

^{13}C: 157.83, 137.06, 128.07, 126.30, 123.48. 78.67, 55.12, 0.45

(1-methoxy-2-phenylprop-1-enyloxy)trimethylsilane two isomers E/Z 60:40 as determined by NMR

E isomer: ^{1}H: 7.33-7.41 (m, 2H), 7.23-7.29 (m, 2H), 7.08-7.14 (m, 1H), 3.62 (s, 3H), 1.95 (s, 3H), 0.02 (s, 9H)

^{13}C: 151.19. 140.94, 128.43, 127.68, 125.12, 56.15, 15.50, -0.04

Z isomer: ^{1}H: 7.33-7.41 (m, 2H), 7.23-7.29 (m, 2H), 7.08-7.14 (m, 1H), 3.50 (s, 3H), 1.91 (s, 3H), 0.28 (s, 9H)

^{13}C: 151.73, 140.46, 127.94, 127.84, 56.65, 16.45, 0.21

(1-methoxy-2,2-diphenylethenyloxy)trimethylsilane

^{1}H: 7.24-7.29 (m, 10H), 3.65 (s, 3H), 0.07 (s, 9H)

^{13}C: 152.89. 140.85, 140.09, 130.86, 130.22, 127.84, 127.80, 125.60, 125.41, 102.49, 56.31, 0.01

(1-methoxy-1,3-pentadienoxy)trimethylsilane mixture of isomers 70:30%

E isomer: ^{1}H: 6.16 (qdd, J=15.4, 10.5, 1.7 Hz, 1H), 5.29 (dqd, J=15.4, 6.7, 0.7 Hz, 1H), 4.44 (d, J=10.5 Hz, 1H), 3.56 (s, 3H), 1.70 (dd, J=6.7, 1.7 Hz, 3H), 0.25 (s, 9H)

^{13}C: 153.58, 125.56, 119.67, 86.76, 54.44, 18.28, -0.24

Z isomer: ^{1}H· 6.16 (qdd J=15.4, 10.3, 1.7 Hz, 1H), 5.30 (dqd, J=15.4, 6.7, 0.6 Hz, 1H), 4.39 (d, J=10.3 Hz, 1H), 3.54 (s, 3H), 1.71 (dd, J=6.7, 1.7 Hz, 3H), 0.22 (s, 9H)

^{13}C: 156.94, 125.96, 118.84, 79.39, 54.70, 18.32, 0.28

(1-methoxynonenyloxy)trimethylsilane

E isomer: ^{1}H: 3.64 (t, J= 8 Hz, 1H), 3.48 (s, 3H), 1.90 (m, 2H), 1.25 (m, 10H), 0.85 (m, 3H), 0.20 (s, 9H)

^{13}C: 153.47, 85.45, 54.85, 31.41, 30.36, 24.38, 23.78, 22.55, 14.11, -0.28

Z isomer: 3.66 (t, J=7.1 Hz, 1H), 3.45 (s, 3H), 1.90 (m, 2H), 1.25 (m, 10H), 0.85 (m, 3H), 0.16 (s, 3H)

^{13}C: 153.47, 85.49, 54.88, 31.82, 30.71, 28.90, 24.47, 23.72, 22.73, 14.15, -0.23

(1-methoxyheptenyloxy)trimethylsilane mixture of isomers E/Z 70:30 as determined by NMR

E isomer: ^{1}H: 3.66 (t, J=7.3 Hz, 1H), 3,51 (s, 3H), 1,94 (m, 2H), 1.28 (m, 6H), 0.88 (m, 3H), 0.22 (s, 9H)

^{13}C: 153.44, 85.45, 54.58, 31.42, 30.38, 24.39. 22.56, 14.13, -0.36

Z isomer: ^{1}H: 3.48 (s, 3H), 3.46 (t, J=7.1 Hz, 1H), 1.93 (m, 2H), 1.27 (m, 6H), 0.88 (m, 3H), 0.19 (s, 9H)

^{13}C: 156.37, 76.40, 54.50, 31.48, 30.63, 24.61, 22.59, 14.13, 0.24

^{1}H and ^{13}C NMR data for the hydroxy esters(in $CDCl_3$ with respect to TMS, 400 MHz)

methyl 2-hydroxy-2-methylpropanoate

^{1}H: 3,73 (s, 3H), 1.39 (s, 6H),

^{13}C: 177.50, 71.84, 52.32, 27.12

methyl 1-hydroxycyclohexane carboxylate

^{1}H: 3.68 (s, 3H), 1.72-1.41 (m, 10H)

^{13}C: 177.53, 52.37, 34.49, 25.01, 20.96,

methyl 2-hydroxy-2-phenylacetate

^{1}H: 7.45-7.28 (m, 5H), 5.17 (s, 1H), 3.71 (s, 3H)

^{13}C: 173.98, 138.17, 128.48, 128.36, 126,49, 72.79, 52.83

methyl 2-hydroxy-2-phenylpropionate

^{1}H: 7.52-7.55 (m, 2H), 7.34-7.22 (m, 3H), 3.71 (s, 3H), 1.77 (s, 3H)

^{13}C: 175.81, 142.65, 128.10, 127.55, 124.95, 75.61, 52.94, 26.61,

methyl 2-hydroxydiphenyl acetate

^{1}H: 7.47-7.44 (m, 2H), 7.36-7,31 (m, 3H), 3.81 (s, 3H)

^{13}C: 174.62, 114.87, 127.83, 127.75, 127.13, 80.39, 53.19

methyl 2-hydroxy-3-pentenoate

^{1}H: 5.89 (dqd, J=15.3, 6.6, 1.5 Hz, 1H), 5.51 (ddq, J=15.3, 6.3, 1.5 Hz, 1H), 4.58 (d, J=16.5 Hz, 1H), 3.77 (s, 3H), 1.72, (ddd, J=6.6, 1.6, 1.2 Hz, 3H)

^{13}C: 174.17, 129,76, 127.23, 71.36, 52.67, 17.63

methyl 4-hydroxy-2-pentenoate

^{1}H: 6.95 (dd, J=15.8, 4.6 Hz, 1H), 6.02 (dd, J=15.8, 1.7 Hz, 1H), 4.47 (m, 1H), 3.72 (s, 3H), 1.31 (d, J=6.7 Hz, 3H)

^{13}C: 151.46, 149.57, 118.96, 66.95, 51.59, 17.63

methyl 2-hydroxynonanoate

^{1}H: 4.09-4.15 (dd, J=8.3, 4.4 Hz,1H), 3.72 (s, 3H), 1.22-1.27 (m, 12H), 0.82 (t, 3H)

methyl 2-hydroxyheptanoate

^{1}H: 4.11-4.17 (dd, J=8.3, 4.4 Hz, 1H), 3.75 (s, 3H), 1.24-1.26 (m, 8H), 0.85 (t, 3H)

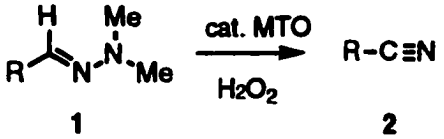
CHAPTER III. THE MTO-CATALYZED OXIDATIVE CONVERSION OF N, N-DIMETHYLHYDRAZONES TO NITRILES

A communication published in *Chemical Communications*

Saša Stanković and James H. Espenson

Methyltrioxorhenium catalyzes the fast and efficient oxidation of aldehyde N, N-dimethylhydrazones to the corresponding nitriles in high yield.

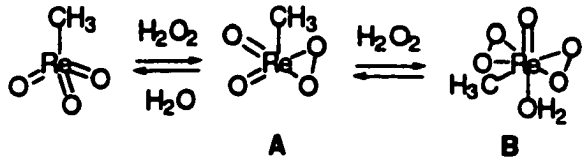
N, N-dimethylhydrazones derived from aldehydes (**1**) can be oxidatively transformed into nitriles (**2**) using hydrogen peroxide as the oxidizing agent and methyltrioxorhenium (CH_3ReO_3, abbreviated as MTO) as the catalyst, usually at the 1% level, as shown in eq. 1. Ten specific examples are presented in **Table 1**.



1 **2** (1)

MTO is a well-established catalyst for oxidations utilizing hydrogen peroxide,[1,2] including oxidations of various nitrogen-containing compounds.[3-7] The reactions were best carried out in acetonitrile-acetic acid-pyridine solvent, 94.5:5:0.5. The use of acetic acid was mandatory since the hydrazones are sufficiently basic to deactivate MTO to the

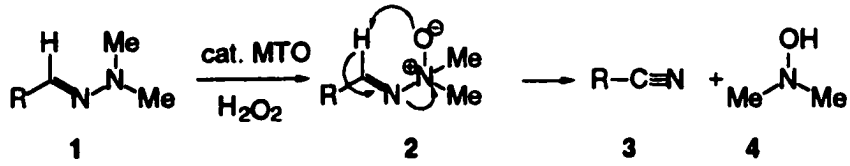
inactive perrhenate.[8] Without pyridine, however, the reaction was accompanied by 5-10% hydrolysis to the parent aldehyde. Hydrolysis can effectively be suppressed by a small amount of pyridine, to reduce the Lewis acidity of MTO and its peroxo adducts. This procedure prevents the hydrolysis of epoxides formed by the oxidation of alkenes by MTO/hydrogen peroxide.[9] Pyridine also accelerates the formation of the catalytically active peroxorhenium complexes as in eq. 2.



(2)

Under the described conditions the hydrazones 1 were completely transformed into the corresponding nitriles after several minutes as indicated by GC/MS analysis. The reaction is quite general: N, N-dimethylhydrazones of aliphatic, unsaturated, aromatic and heterocyclic aldehydes were successfully oxidized to the corresponding nitriles. Other present oxidizable functionalities did not interfere; see entry 8 where the hydrazone was oxidized without the pyridine-N-oxide being formed. In this particular example pyridine was not used, since the starting hydrazone itself functions in this regard. Also in entry 10, as expected, the double bond was not epoxidized during the reaction, indicating far greater reactivity of the hydrazone moiety compared to the double bond.

The oxidation of **1** presumably goes through the oxide **2**, which undergoes a Cope-type elimination[15] to yield the nitrile **3** and dimethylhydroxylamine **4**, eq. 3. N,N-Dialkylhydroxylamines are known to undergo oxidation to nitrones with H_2O_2/MTO.[7] No attempts were made to detect either dimethylhydroxylamine or is oxidation product.



(3)

N,N-Dialkylhydrazones are versatile and useful intermediates in organic synthesis, especially in carbon-carbon bond forming reactions,[10] which has led to considerable interest in the development of mild methods for their transformation into nitriles. Non-oxidative procedures *via* N,N,N-trimethylhydrazonium salts or directly, in hyperbasic media,[11,12] have been used, but they require high temperatures and strong bases. Several mild oxidative procedures for the use of hydrogen peroxide, using 3-chloroperbenzoic acid and magnesium monoperoxyphtalate, have been reported.[13-15] These reactions, however, are rather slow; for example, the 3-chloroperbenzoic acid reactions require several hours.

Hydrogen peroxide is a desirable reagent on several counts. Selenium dioxide and 2-nitrobenzeneselinic acid catalyze its reactions,

giving good yields of nitriles from aromatic and unsaturated N,N-dimethylhydrazones, but hours, even days, are required. Moreover, these catalysts give poor results with aliphatic N,N-dimethylhydrazones which are largely hydrolyzed. Phosphomolybdic acid, $H_3PO_4 \cdot 12MoO_3 \cdot 12H_2O$, performs better with aliphatic hydrazones but it gives by products such as the corresponding acids. Compared to these catalysts, MTO is clearly superior. MTO also catalyzes the oxidative cleavage of ketone hydrazones to the parent carbonyl compounds; these reactions are now being investigated.

A typical experimental procedure is as follows: **1** (10 mmol) was added to a rapidly stirred solution of MTO (1 mM), hydrogen peroxide (0.3 M, added as 30% solution in water), pyridine (25 mM) in 100 mL of acetonitrile containing 5 vol% HOAc. After 15 min., most of the acetonitrile was removed by rotary evaporation, and the residue poured into 300 mL of ether, washed successively with 0.1 M HCl and satd. sodium bicarbonate. (In the case of 4-cyanopyridine, entry 8, the ether solution was washed only once with satd. sodium bicarbonate.) The ethereal solution was then dried over anhydrous sodium sulfate, and the product obtained after evaporation. The crude nitriles were purified by column chromatography (n-hexane/acetone).

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Table 1. Preparation of Nitriles from Aldehyde N,N-dimethylhydrazones[a]

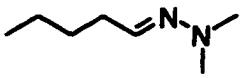
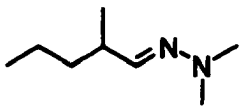
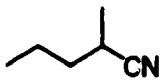
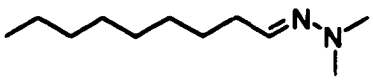
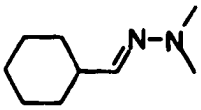
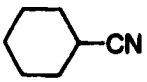
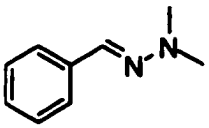
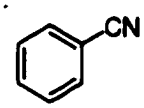
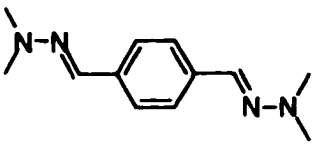
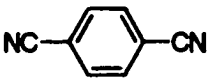
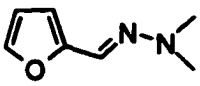
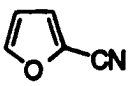
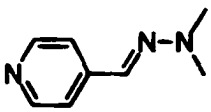
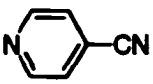
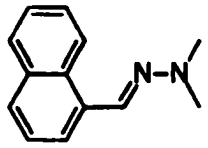
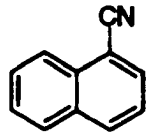
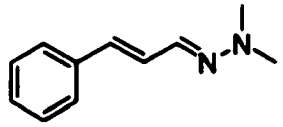
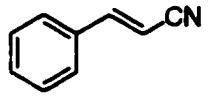
Entry	Hydrazone	Product	Yield[b]
1			88%
2			90
3			92
4			95
5			93
6			94
7			93
8			92[c]

Table 1. (continued)

Entry	Hydrazone	Product	Yield[b]
9			94
10			91

[a] With 10 mM substrate, 300 mM H_2O_2, 25 mM pyridine and 1 mM MTO in acetonitrile, acetic acid, pyridine (94.5:5:0.5) in 15 min time; [b] isolated yield; [c] without pyridine

Supporting Information

^{1}H and ^{13}C NMR data for the different hydrazones ($CDCl_3$)

Hydrazone	^{1}H NMR: ppm	13C NMR:ppm
pentanal N,N-dimethylhydrazone	6.54 (t, 1H), 2.60 (s, 6H), 2.08-2.15 (m, 2H), 1.18-1.39 (m, 4H), 0.79 (t, 3H)	139.87, 43.39, 32.75, 29.90, 22.26, 13.89
2-methylpentanal N,N-dimethylhydrazone	6.37 (d, 1H), 2.59 (s, 6H), 2.18-2.27 (m, 1H), 1.17-1.30 (m, 4H), 0.92 (d, 3H), 0.78 (t, 3H)	144.89, 43.41, 37.73, 36.85, 20.26, 18.95, 14.11
nonal N, N-dimethylhydrazone	6.55 (t, 1H), 2.60 (s, 6H), 2.07-2.14 (m, 2H), 1.15-1.37 (m, 12H), 0.76 (t, 3H)	140.50, 43.39, 33.05, 31.80, 29.39, 29.17, 27.76, 22.61, 14.05
cyclohexanecarboxaldehyde N, N-dimethylhydrazone	6.40 (d, 1H), 2.59 (s, 6H), 2.01-2.13 (m, 1H), 1.50-1.67 (m, 4H), 1.06-1.26 (m, 6H)	144.06, 43.25, 41.27, 31.28, 25.92, 25.59

2-furaldehyde N,N-dimethylhydrazone	7.26 (dd, 1H), 7.00 (s, 1H), 6.28 (dd, 1H), 6.25 (dd, 1H), 2.83 (s, 6H)	151.95, 141.76, 123.16, 111.12, 107.07, 42.62
4-pyridinecarboxaldehyde N,N-dimethylhydrazone	8.45 (d, 2H), 7.34 (d, 2H), 6.95 (s, 1H), 3.02 (s, 6H)	149.79, 144.30, 126.95, 119.39, 42.37
tereftalaldehyde N,N-dimethylhydrazone	7.50 (s, 4H), 7.21 (s, 2H), 2.95 (s, 12H)	132.82, 125.73, 42.86
benzaldehyde N,N-dimethylhydrazone	7.61 (d, 2H), 7.36 (t, 2H), 7.26 (s, 1H), 7.23 (t, 1H), 2.96 (s, 1H)	136.68, 132.73, 128.30, 127.17, 125.44, 42.64
1-naphtalenecarboxaldehyde N,N-dimethylhydrazone	8.56 (dd, 1H), 7.92 (s, 1H), 7.85-7.89 (m, 2H), 7.76 (d, 1H), 7.45-7.57 (m, 3H), 3.08 (s, 6H)	133.91, 132.25, 131.11, 130.49, 128.59, 127.67, 125.96, 125.59, 125.49, 124.08, 123.75, 42.86
(E)-cinnamaldehyde N, N-dimethylhydrazone	7.40 (d, 2H), 7.30 (t, 2H), 7.20 (t, 1H), 7.12 (d, 1H), 6.95 (q, 1H), 6.60 (d, 1H), 2.90 (s, 6H)	137.18, 135.10, 131.55, 128.52, 127.42, 127.26, 126.09, 42.62

CHAPTER IV. OXIDATIVE CLEAVAGE OF N,N-DIMETHYLHYDRAZONES TO KETONES WITH HYDROGEN PEROXIDE, CATALYZED BY METHYLTRIOXORHENIUM(VII)

A paper submitted to *The Journal of Organic Chemistry*

Saša Stankovic′ and James H. Espenson

Abstract

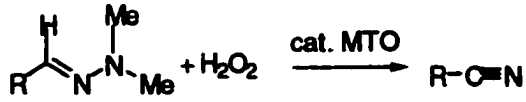
N,N-dimethylhydrazones derived from ketones revert to the parent ketones when treated with hydrogen peroxide in the presence of the catalyst methyltrioxorhenium(VII). Isolated yields of 85-98% were obtained for reactions run in acetonitrile-acetic acid (95:5) on the 2.5 mmol scale. Kinetics experiments were carried out for four substituted benzophenone hydrazones. The reactions followed first-order kinetics with respect to the substrate and first-order with respect to total catalyst. The rate was independent of the peroxide concentration under the conditions used, which employed 0.2 M hydrogen peroxide, because the catalyst was entirely in the form of the diperoxo complex $CH_3ReO(\eta^2\text{–}O_2)_2(H_2O)$. The second-order rate constants (L mol^{-1} s^{-1} at 25 °C in 95:5 acetonitrile-acetic acid) for reactions of the compounds $(XC_6H_4)_2C{=}NNMe_2$ are: 127 (X = 4,4'-CH_3), 85 (H), 44.5 (3,3'-CF_3), and 27.9 (3,3'-NO_2). According to an analysis by the Hammett equation, $\rho = -0.72$.

Isotopic labeling with $H_2{}^{18}O$ added (with urea-hydrogen peroxide used to avoid another source of water), the acetophenone formed from acetophenone hydrazone showed a 20% level of oxygen–18. This level remained invariant when the catalyst was ten-fold lower. This suggests competing oxidation steps with competing pathways to oxaziridine (20%) and dimethylamine oxide (80%) intermediates.

Introduction

N,N-Dialkylhydrazones are valuable derivatives in synthetic organic chemistry especially as sources of carbanions. They serve as equivalents of carbanions derived from aldehydes and ketones in electrophilic substitutions. The final stages of chemical manipulation frequently require their cleavage, so as to regenerate the parent carbonyl compound. To do so, a number of procedures have been developed, both hydrolytic and oxidative.[1]

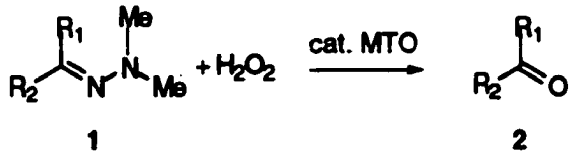
By way of preface, it should be noted that hydrogen peroxide, catalyzed by methyltrioxorhenium (CH_3ReO_3 or MTO), converts N,N-dimethylhydrazones derived from aldehydes into nitriles:[2,3]



(1)

We have now used the same reagents for N,N-dimethylhydrazones derived from ketones. In this case, the hydrazone

reverts to the parent carbonyl compound, eq. 2. Herein we report the effectiveness of this reaction as well as certain kinetics and isotopic tracer experiments pertaining to its mechanism.



(2)

Experimental Section

Reagents. The ketone hydrazones were prepared by either of two methods. Aliphatic hydrazones were prepared by mixing the ketone with three equiv. of 1,1-dimethylhydrazine without solvent at room temperature. The progress of this reaction was monitored either by TLC or GC/MS. The reactions were typically complete in 30 min; the reaction mixture was dissolved in ether and then washed and dried. Crude hydrazones were obtained after solvent removal. For the less reactive aromatic ketones a more vigorous procedure was required. The ketone (50 mmol) and N,N-dimethylhydrazine (75 mmol) were dissolved in benzene (20 mL). Two or three drops of trifluoroacetic acid were added and the mixture refluxed with continuous removal of water using a Dean-Stark trap. Depending on the nature of the ketone, the reaction

times ranged from several hours to several days. The hydrazones were purified either by distillation or column chromatography.

Oxidative cleavage of hydrazones. The ketone hydrazone (2.5 mmol) was added dropwise via syringe to a cooled (0 °C) and well-stirred solution of acetonitrile–acetic acid 95:5, hydrogen peroxide (7.5 mmol) and MTO (0.025 mmol). The addition took approximately 5 min, after which the reaction mixture was allowed to warm to room temperature during the next 5-10 min. The mixture was then poured into dichloromethane and washed with saturated sodium bicarbonate solution. The dichloromethane extract was dried over anhydrous sodium sulfate. After filtration and solvent removal, most ketones were colored but otherwise pure as determined by GC/MS. Additional purification was achieved by flash chromatography through a short column (petroleum ether/acetone).

Kinetics. Experiments were carried out with substituted benzophenone hydrazones, the least reactive of these substrates, to simplify the measurements. The choice of a medium was critical because the inherent basicity of the hydrazones[4] deactivates the MTO catalyst.[5,6] Our experiments used a 95:5 mixture of acetonitrile and acetic acid. To protect MTO and its peroxo complexes, 25 mM pyridine was introduced into the reaction mixture.[7,8] Other concentrations were: 0.2 M hydrogen

peroxide and 1 mM ketone hydrazone. The reaction was followed spectrophotometrically in quartz cuvettes of 1 cm optical path. The runs were performed under air (which has no effect) at 23 °C. The MTO solutions used in these experiments was freshly prepared.

The procedure used for kinetics was as follows: all ingredients save the catalyst and substrate were mixed in the cuvette, giving total volume of 3.0 mL. The catalyst was then added, and after 30 s the substrate was introduced. The decrease in absorbance at 430 nm, corresponding to the decrease in the concentration of the ketone hydrazone, was recorded with time. The absorbance-time curves were analyzed by the nonlinear least-squares method, to obtain the pseudo-first-order rate constant according to the equation:

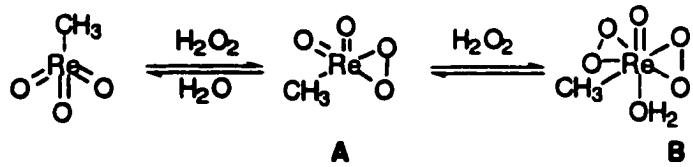
$$Abs_t = Abs_\infty + (Abs_0 - Abs_\infty) \cdot e^{-k_\psi t} \quad (3)$$

Isotopic labeling. These experiments were performed in the following manner. Urea hydrogen peroxide was used to avoid isotopic dilution. UHP (0.3 mmol), ^{18}O-labeled water (90% ^{18}O, 0.03 mL) and pyridine (0.1 mmol) were mixed in 1.0 mL acetonitrile. Acetic acid was not added in these experiments. Catalyst was added, 0.001 mmol, followed by acetophenone hydrazone (0.025 mmol). After two minutes, the sample was diluted 200-fold with acetonitrile. A small sample was then injected

into the GC/MS instrument. A separate experiment was done with ten-times higher catalyst concentration. The ratio of the signals at m/z 105 and 105 in the MS spectrum of acetophenone was monitored. A control experiment was performed with acetophenone itself, and it showed no incorporation of ^{18}O on this time scale.

Results

Peroxorhenium intermediates. The active forms of the catalyst are peroxorhenium complexes, designated **A** and **B**. As shown in eq. 4, they are in equilibrium with MTO, H_2O_2 and one another. These steps are, however, not always rapid relative to the ones involved in catalysis.[9]



(4)

Reaction conditions and yields. Ketone hydrazones were oxidized by the MTO/H_2O_2 system in a solvent mixture composed of acetonitrile and acetic acid in a 95:5 ratio. Because the hydrazones are basic, acetic acid is helpful in stabilizing MTO against decomposition to the catalytically-inactive perrhenate ion.[5] Acetic acid is, however, insufficiently acidic to protonate the hydrazones which would render them inactive toward **A** or **B**. The oxidations are so exothermic on a preparative scale that it was

necessary to cool the reaction to 0 °C, and slowly introduce the hydrazone into the reaction mixture. Cooling also stabilizes MTO, allowing these reactions to be performed with 1% of catalyst relative to the hydrazone. Under these conditions, the ketones were formed in a matter of minutes. Specific data are given in **Table 1**.

Kinetics. Hydrazones are noted for their nucleophilicity.[10] It came as no surprise, then, that they are reactive substrates towards MTO/hydrogen peroxide. The conditions of the experiments were designed to permit a simple measurement of the rate constant for the one reaction between substrate and **B**. To do so, 0.2 M hydrogen peroxide was used so that **B** was the only significant species of those in eq. 4. Also, and just as important, one must ensure that the reaction between **A** and hydrogen peroxide is accelerated, to ensure that this reaction does not become rate-controlling; the 25 mM pyridine present in the kinetics provides the necessary acceleration of the peroxide binding step, as demonstrated previously.[8] The rate law is:

$$-\frac{d[Ar_2C=NNMe_2]}{dt} = k_4[Ar_2C=NNMe_2]\cdot[Re]_T \tag{5}$$

Different tests were performed to demonstrate the correctness of this equation. Experiments at several concentrations of hydrogen peroxide, 0.1–0.3 M, showed that the rate constant is independent of its

concentration. The kinetics data gave excellent fits to first-order kinetics in each experiment. A few experiments at different concentrations for one substrate, benzophenone hydrazone, 0.5–5 mM. For each compound the variation of k_ψ against $[Re]_T$, which is essentially [B], was a straight line that passed through the origin. The slopes of these lines are the values of k_4, the values of which are summarized in **Table 2**.

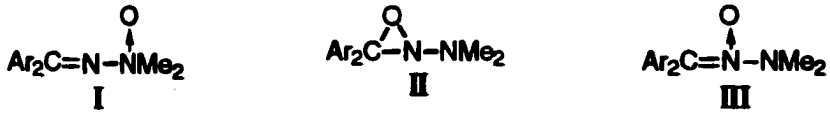
Isotopic labeling. To learn more about the intermediates in this reaction, experiments were performed to measure the extent to which the carbonyl oxygen of the produced acetophenone incorporates oxygen-18 from water added at the start of the experiment. Some 20% of the resulting acetophenone was ^{18}O-labeled. This experiment, first performed with 0.010 mM MTO, was then repeated with about 1/10-that level of catalyst. The second experiment also gave 20% ^{18}O incorporation. This result shows that the partitioning of the intermediate along a different course does not occur in a step in which there is competition between oxidation and hydrolysis steps. This issue will be taken up in a subsequent section.

Discussion

Kinetics. Comparing this pattern to others found,[9,11] we conclude that this reaction resembles others in which an electron-rich substrate is

oxidized by peroxorhenium complexes. On that basis, one imagines that a nucleophilic center of the ketone hydrazone attacks a peroxo oxygen of **B**. The electronic requirements can be inferred from the quantitative kinetics effect of substituents on the aromatic rings of substituted benzophenone hydrazones. The data in **Table 2** were analyzed according to the Hammett equation. As shown in **Figure 2**, the plot of log k_4 against σ is linear (correlation coefficient 0.999). Its slope is the reaction constant, $\rho = -0.72$. The substantial negative value supports the model proposed, in that the reaction center (either or both of the N atoms) becomes more positive in the transition state that it was at the outset.

Molecular mechanism. MTO activates hydrogen peroxide in such a way that one oxygen atom of the peroxorhenium intermediate is transferred to the substrate in the transition state. The first transition state, corresponding from O-atom transfer from **B** to the substrate, is the rate-controlling process. This substrate offers, in principle, at least three options for the next species produced from it. The three are depicted as follows:



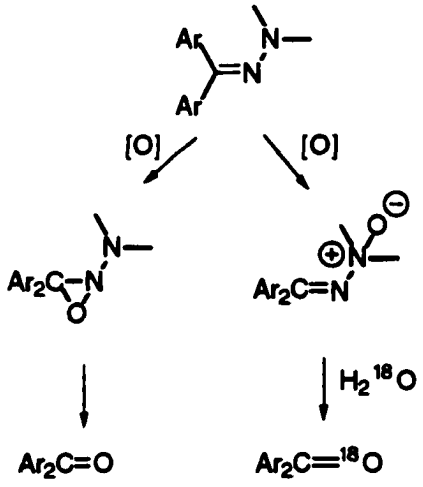
Structure **I** was proposed to account for the reaction of *aldehyde* hydrazones.[2,3] It is consistent with the simple transfer of an oxygen to the

most basic site. This intermediate is, however, incapable of carrying the reaction further, at least in the same manner as the aldehyde derivatives, in that dimethylhydroxylamine cannot be eliminated through hydrogen abstraction. On the other hand, the formation of alternative II (directly or via III) as the sole pathway cannot account for the data, even though it might partition between oxidation (80%, to account for the ^{18}O labeling result) and hydrolysis (20%), because the stage at which an intermediate partitions must either be the one with two competing oxidations or two hydrolyses. That feature is required by the finding of 20% ^{18}O incorporation, irrespective of a ten-fold lowering of the MTO concentration.

On that basis, we have formulated a mechanism (**Scheme 1**) in which the reaction partitions to I and II in its initial oxidation stage. (The fact that the slowest step is the one that features partitioning is also plausible, in that its rate constant is the smallest in the sequence). Intermediate I, in light of its polarity, will solvolyze. With $H_2{}^{18}O$ present, $Ar_2C{=}^{18}O$ will result. We take this to indicate that the oxidation proceeds initially to I 20% of the time; any other formulation would have further but undocumented partitioning steps which we have not incorporated (Occam's razor). The majority of the reaction, 80%, proceeds via II. Its oxidation yields unlabeled ketone, since the peroxide source had only ^{16}O.

Organonitrogen compounds are oxidized by the H_2O_2/MTO, often in a complex sequence of reactions. Consider dimethylhydroxylamine, for example, which may be an intermediate. It is oxidized in several steps to a nitrone.[12] The oxidation products of the nitrogen part of the ketone were not investigated, because it seemed little new information would result.

Scheme 1



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Acknowledgment

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Table 1 Oxidative cleavage of ketone hydrazones

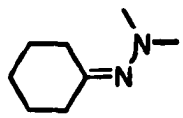
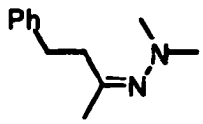
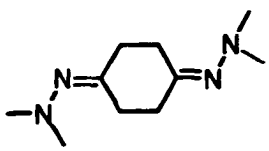
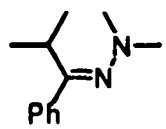
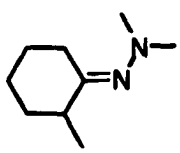
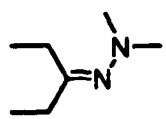
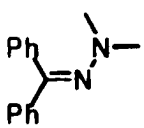
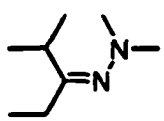
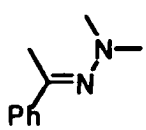
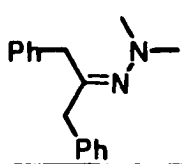
Hydrazone	% Yield	Hydrazone	% Yield
	85		92
	88		90
	89		85
	98		87
	95		93

Table 2. Rate constants for the bimolecular reaction between substituted benzophenone hydrazones and $CH_3Re(O)(\eta^2\text{–}O_2)_2(H_2O)$, **B** [a]

$(X_2C_6H_3)_2C{=}NNMe_2$ X =	k_4/L mol^{-1} s^{-1}
4,4'–MeO	127 ± 4
H	85 ± 1
3,3'–CF_3	44.5
3,3'–NO_2	27.9 ± 0.4

[a] In acetonitrile-acetic acid (95:5) in the presence of 25 mM pyridine at 25 °C.

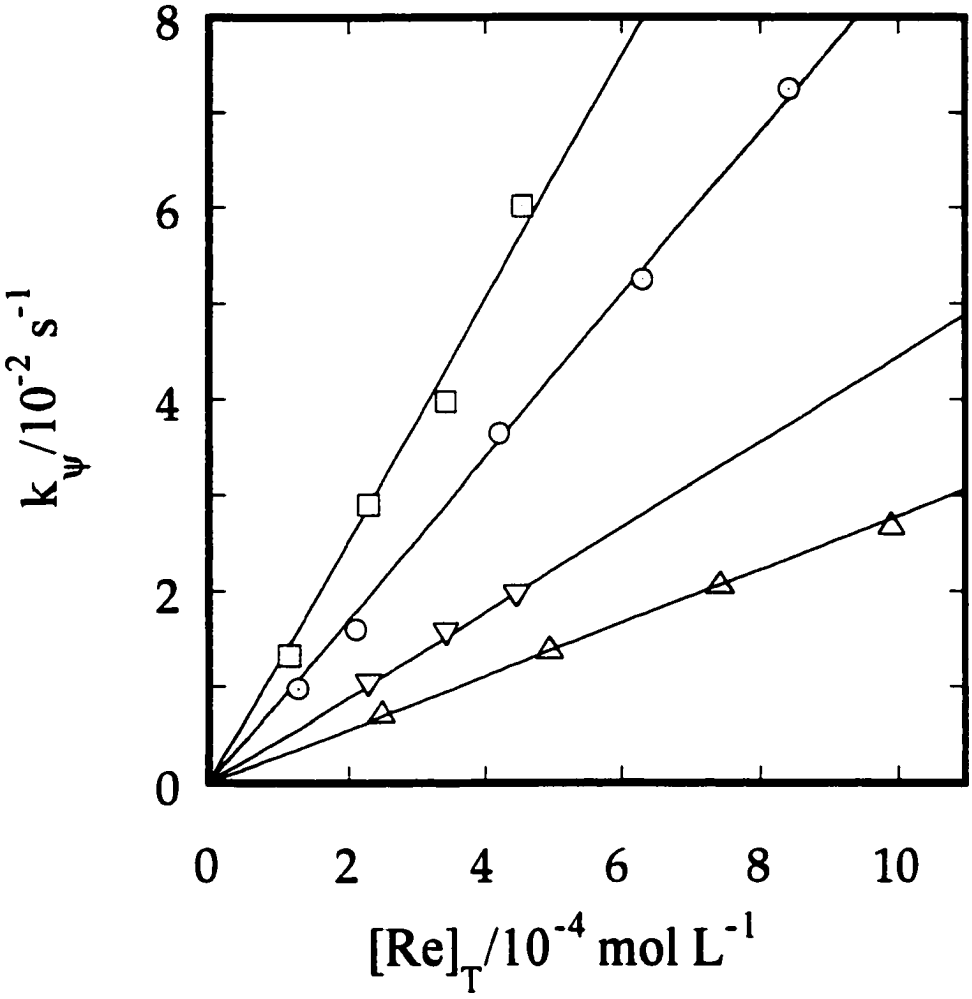


Figure 1. The pseudo-first order rate constants (at 25 °C in 95:5 acetonitrile: acetic acid) for the oxidation of substituted benzophenone hydrazones vary linearly with the total concentration of the rhenium catalyst. In order of decreasing slope the data for $(XC_5H_3)_2C{=}N{-}NMe_2$ refer to X = p-MeO, H, m–CF_3, and m-NO_2.

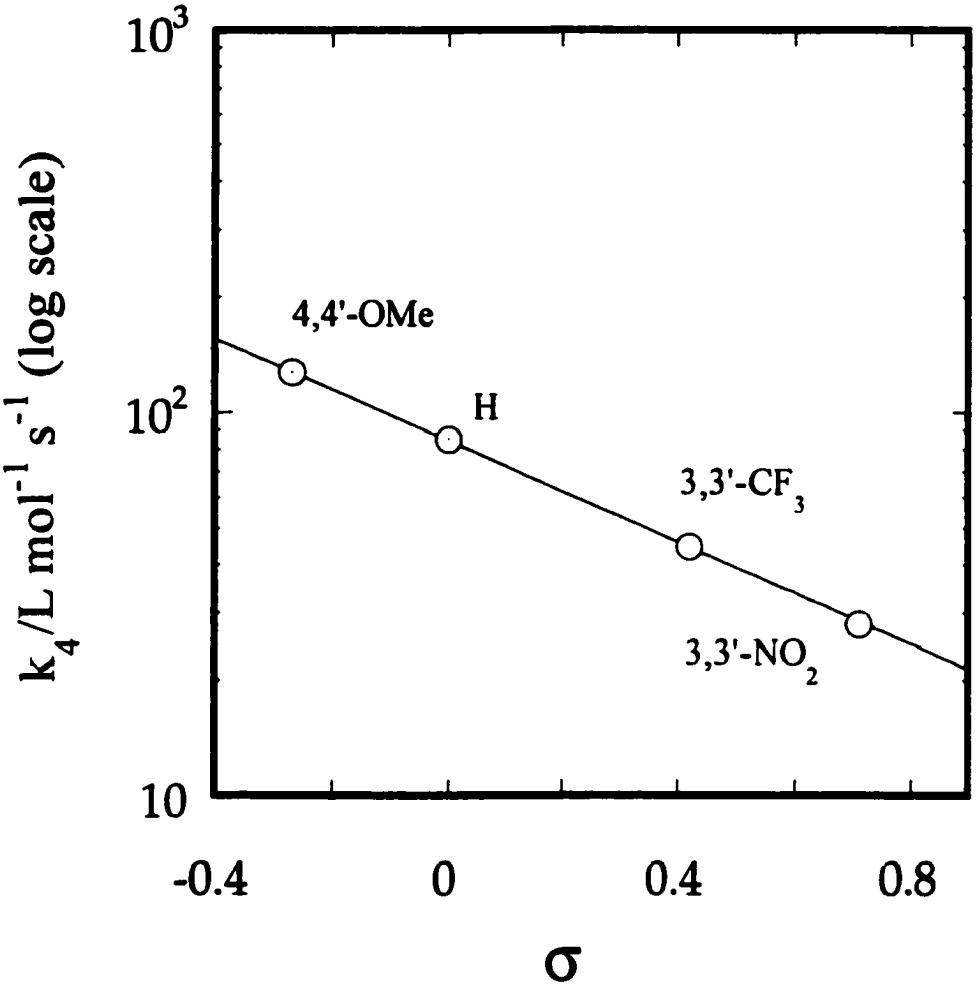


Figure 2. A linear-free-energy correlation of the kinetic data for the oxidation of substituted benzophenone hydrazones with the peroxorhenium compound **B**, $CH_3ReO(\eta^2\text{-}O_2)_2(H_2O)$ against the Hammett substituent constant σ.

Supporting Information

^{1}H-NMR Spectra (in $CDCl_3$, chemical shifts with respect to $SiMe_4$)

Ketone Hydrazone	^{1}H	^{13}C
4,4'-dimethoxybenzophenone N,N-dimethylhydrazone	7.42 (d, 2H), 7.32 (d, 2H), 6.91 (d, 2H), 6.80 (d, 2H), 2.82 (s, 3H), 2.77 (s, 3H), 2.49 (s, 6H)	160.32, 159.23, 157.62, 132.58, 130.31, 129.31, 129.12, 55.12, 55.40, 47.00
cyclohexanone N,N-dimethylhydrazone	241 (t, 2H), 2.34 (s, 6H), 2.14 (t, 2H), 1.50-1.62 (m, 6H)	170.00, 47.53, 35.95, 28.59, 27.43, 26.58, 25.97
2-methylcyclohexanone N,N-dimethylhydrazone	2.53 (m, 1H), 2.35 (s, 6H), 2.33 (m, 2H), 1.35-1.77 (m, 6H), 1.03 (d, 3H)	172. 65, 47.44, 38.77, 34.78, 26.84, 26.55, 23.07, 17.86
4-phenyl-2-butanone N,N-dimethylhydrazone	7.24 (m, 2H), 7.16 (m, 3H), 2.76-2.88 (m, 2H), 2.46-2.52 (m, 2H), 2.38, (s, 6H), 1.92 (s, 3H)	166.82, 141.06, 128.33, 128.28, 128.19, 47.30, 40.41, 33.10, 16.87
3-pentanone N,N-dimethylhydrazone	2.27 (q, 2H), 2.24 (s, 6H), 2.07 (q, 2H), 0.92 (t, 6H)	174.60, 47.11, 28.33, 22.36, 11.28, 10.73

2-methyl-3-pentanone N,N-dimethylhydrazone	2.34 (s, 6H), 2.32 (sep, 1H), 2.19 (q, 2H), 1.09 (d, 3H), 1.03 (t, 3H)	176.58, 47.33, 38.46, 27.82, 19.03, 11.52,
1,4-cyclohexanedione N,N-dimethylhydrazone[1]	2.56 (m, 4H), 2.37 (m, 4H), 2.32 (s, 12H)	167.33, 167.09, 47.16, 47.04, 33.49, 32.40, 26.65, 25.58
3,3'-dinitrobenzophenone N,N-dimethylhydrazone	8.05-8.20 (m, 4H), 7.75 (m, 3H), 7.42 (t, 1H), 2.66 (s, 6H)	170.53, 148.31, 144.55, 140.99, 137.79, 135.32, 132.53, 129.83, 129.04, 124.16, 123.65, 122.90, 121.53, 47.53
3,3'-bis(trimethylfluoro)benzophenone N,N-dimethylhydrazone	7.79 (s, 1H), 7.66 (m, 1H), 7.33 (s, 1H), 7.55 (m, 3H), 7.46, (d, 1H), 7.37 (t, 1H), 2.60 (s, 6H)	193.67, 148.71, 140.36, 137.38, 132.66, 130.52, 129.12, 128.52, 126.02, 125.48, 125.35, 125.25, 125.03, 123.82122.77, 122.54, 47.18
benzophenone N,N-dimethylhydrazone	7.48 (m, 2H), 7.39 (m, 4H), 7.29 (m, 2H), 2.55 (s, 6H)	178.58, 139.74, 137.12, 128.96, 128.70, 128.25, 128.18, 127.79, 127.69, 47.19

acetophenone N,N-dimethylhydrazone	7.72 (m, 2H), 7.24 (m, 3H), 2.59, (s, 6H), 2.34 (s, 3H)	162.14, 139.14, 129.28, 128.31, 126.43, 47.31, 15.63
1,3-diphenylacetone N,N-dimethylhydrazone	7.20-7.35 (m, 3H), 7.10-7.15 (m, 2H), 3.62 (s, 2H), 3.58 (s, 2H), 2.36 (s, 6H)	176.50, 142.58, 141.36, 130.47, 129.82, 129.37, 128.99, 127.43, 127.02, 60.33, 58.15, 47.23
isobutyrophenone N,N-dimethylhydrazone	7.33 (m, 3H), 7.16 (m, 2H), 2.75 (septet, 1H), 2.31 (s, 6H), 1.05 (d, 6H)	169.14, 137.75, 127.91, 127.47, 127.00, 47.17, 36.95, 20.49

[1] The compound is a mixture of almost equimolar amounts of isomers.

GENERAL CONCLUSION

Pyridine exhibits dramatic effect on the outcome of oxidation of silyl enol ethers. While without pyridine present the mentioned starting materials are hydrolyzed, for all practical purposes instantaneously, to the parent ketones, in its presence their hydrolysis is almost entirely suppressed. The rapid procedure described in this thesis also requires the presence of acetic acid to buffer the reaction system and enable the reaction to be performed with an economical catalyst level. Presently, the method described in this thesis appear to be the best thus far available in the literature for the oxidation of silyl enol ethers with aqueous hydrogen peroxide.

Ketene acetals, owing to the presence of an additional alcoxy functionality require a more careful approach. Aqueous hydrogen peroxide has to be replaced with an anhydrous source of hydrogen peroxide, urea hydrogen peroxide addition compound. In addition the reaction has to be performed at low temperature with gradual introduction of the water labile substrate to the reaction mixture, all in order to minimize its exposure to the detrimental reaction medium and to reduce the extent of catalyst decomposition. The described method is

the first successful one for the oxidation of this class of compounds with hydrogen peroxide.

The MTO/hydrogen peroxide catalytic system appears to be one of the best for the oxidative conversion of N, N-dimethylhydrazones derived from aldehydes to the corresponding nitriles. The short reaction times, comparatively mild conditions, demonstrated broad functional group tolerance and nearly quantitative yields render it competitive with the methods presently available in the literature for achieving the given transformation.

N, N-dimethylhydrazones derived from ketones, notorious for their stability towards simple hydrolysis are oxidatively cleaved to the parent ketones under comparatively mild conditions with the mentioned catalytic system. Even though it has been established that the reaction is electrophylic in nature, presently is very little known about its exact mechanism. In spite of this uncertainty, from the synthetic point of view this method represents a step forward of the given catalytic system into the world of synthetic chemistry.

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