Notes

Oxidative Cleavage of *N,N*-Dimethylhydrazones to Ketones with Hydrogen Peroxide, Catalyzed by Methyltrioxorhenium(VII)

Saša Stanković and James H. Espenson*

Ames Laboratory and Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa 50011

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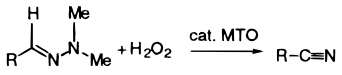
Introduction

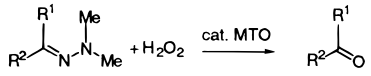
N,N-Dialkylhydrazones are valuable derivatives in synthetic organic chemistry, especially as sources of carbanions. They serve as equivalents of carbanions derived from aldehydes and ketones in electrophilic substitutions. The final stages of chemical manipulation frequently require their cleavage, so 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.



1 2 (2)

Experimental Section

Reagents. The ketone hydrazones were prepared by either of two methods. Aliphatic hydrazones were prepared by mixing the ketone with 3 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 a 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:

$$\mathrm{Abs}_t = \mathrm{Abs}_\infty + (\mathrm{Abs}_0 - \mathrm{Abs}_\infty)e^{-k_\psi t}$$

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 of acetonitrile. Acetic acid was not added in these experiments. Catalyst was added, 0.001 mmol, followed by acetophenone hydrazone (0.025 mmol). After 2 min, 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 10-times higher catalyst concentration. The ratio of the signals at *m/z* 105 and 107 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.

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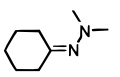
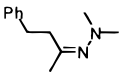
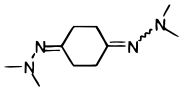
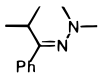
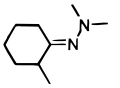
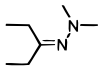
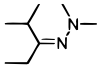
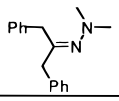
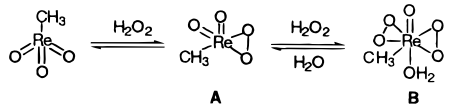
Table 1. Oxidative Cleavage of Ketone Hydrazones

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

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 that 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 toward 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:

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

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 were carried out 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 (Figure 1). 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.

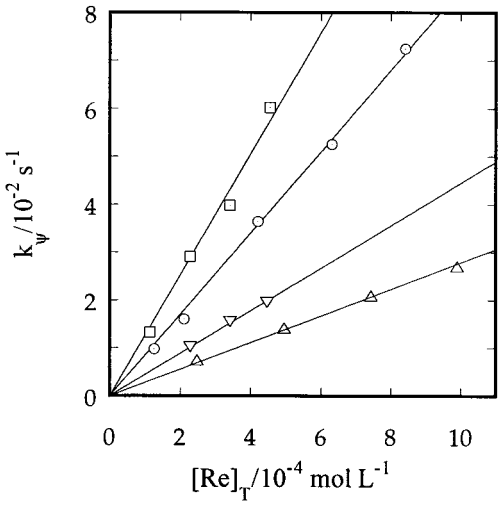


Figure 1. Pseudo-first-order rate constants (at 25 °C in 95:5 acetonitrile/acetic acid) for the oxidation of substituted benzophenone hydrazones vary linearly with the total concentration of the rhenium catalyst. In order of decreasing slope the data for $(XC_6H_4)_2C{=}NNMe_2$ refer to X = *p*-MeO, H, *m*-CF_3, and *m*-NO_2.

Table 2. Rate Constants for the Bimolecular Reaction between Substituted Benzophone 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.

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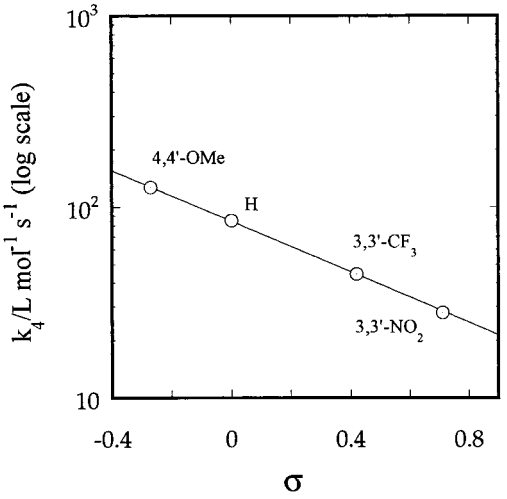
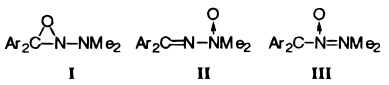


Figure 2. Linear free energy correlation of the kinetic data for the oxidation of substituted benzophenone hydrazones with the peroxorhenium compound **B**, $CH_3ReO(\eta^2\text{-}O_2)_2(H_2O)$ against the Hammett substituent constant σ.

Discussion

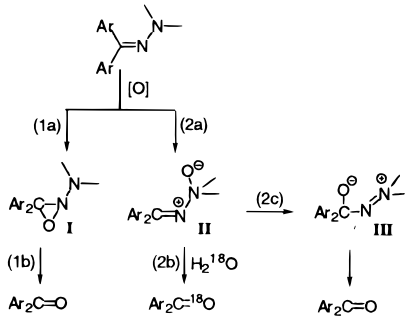
Kinetics. Comparing this pattern to others found,[9,11] we conclude that this reaction resembles others in which an electron-rich substrate is oxidized by peroxorhenium complexes. On that basis, one imagines that a nucleophilic center of the ketone hydrazone attacks a peroxo oxygen of **B**. The electronic 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 than 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 to O-atom transfer from **B** to the substrate, is the rate-controlling process. This substrate offers, in principle, at least three options for the intermediate(s) produced from it. The three are depicted as follows:



Structure **II** 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. It may, of course, react in another way. On the other hand, the formation of alternative **I** (directly or via **III**) as the sole pathway cannot account for the data, even though

Scheme 1



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 hydrolysis or rearrangement steps. That feature is required by the finding of 20% ^{18}O incorporation, irrespective of a 10-fold lowering of the MTO concentration. As a result, either the competing pathways are both oxidations or neither is.

On that basis, several mechanistic possiblities can be seen, Scheme 1. The reaction may partition to **I** and **II** in the initial oxidation stage, steps 1a and 2a. An attractive feature of this assignment is that partitioning resides in the slowest (rate-controlling) stage, which should be the most selective. Intermediate **II** should solvolyze; with $H_2{}^{18}O$, $Ar_2C{=}{}^{18}O$ will result. If these assignments are correct, then 80% of oxidation leads to **I**, giving unlabeled ketone, as in step 1b. Arguing against these assignments are two findings: (a) the linearity of the Hammett LFER and (b) the well-documented mechanism operable in the case of aldehyde *N*,*N*-dimethylhydrazones. The Hammett plot, where the experimental rate constant is the *sum* of those for steps 1a and 2a, would show distinct curvature unless the two ρ values were coincidentally the same. Indeed, we have previously encountered one instance where exactly that was found when parallel pathways for the oxidation coexisted.[12] It is a particularly telling point that the oxidation occurs exclusively at the dimethylamino nitrogen of aldehyde *N*,*N*-dimethylhydrazones.[3] There is no plausible basis for imagining that a ketone hydrazone would be different.

We therefore propose a different sequence of steps, which are included as a part of Scheme 1. The initial oxygen-atom transfer is proposed to occur exclusively at the dimethylamino nitrogen, just as with the aldehyde-derived hydrazones. The reaction yields intermediate **II**, which can partition to hydrolysis to a ketone (labeled with $H_2{}^{18}O$) or rearrange. The rearrangement of **II** to **III** may be a 1,3-shift or, perhaps less plausibly, two 1,2-shifts. In any event, this leads to (unlabeled) ketone. It is the partitioning of **II** between hydrolysis and rearrangement that gives rise, in this model, to the partial incorporation of the oxygen-18 label from the solvent. Much less likely, **II** might itself be further oxidized, but this is not likely in that the addition of one oxygen atom always reduces greatly the propensity for further oxidation.

The ultimate fate of the nitrogen part of the hydrazones was not examined. Certainly, a mixture of oxidation products could be found. Organonitrogen compounds

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are oxidized by the H_2O_2/MTO, often in a complex sequence of reactions. Consider dimethylhydroxylamine, for example, which may be an intermediate in this chemistry. It is oxidized in several steps to a nitrone.[13] The oxidation products of the nitrogen part of the ketone were not investigated, because it seemed little new information would result.

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Supporting Information Available: Tables of ^{1}H and ^{13}C NMR chemical shifts are presented. This material is available free of charge via the Internet at http://pubs.acs.org.

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