Selective deoximation using alumina supported potassium permanganate[†]

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Abstract—Ketoximes are converted to the parent ketones in good yields when treated with potassium permanganate supported on neutral alumina (ASPP). An optimized procedure has been developed, the simple work-up minimizes loss of product and oximes have been selectively oxidized in the presence of alkenes. © 2001 Elsevier Science Ltd. All rights reserved.

Oximes are useful to organic chemists as protecting groups,[1] and as synthetic intermediates en route to amines[2] and nitriles.[3] Many oxidations of oximes have been reported, including some using potassium permanganate in aqueous media.[4,5] Many oxidative deoximations have appeared in recent years.[6] Each reagent represents a different balance of yield, toxicity, expense, selectivity, technique and convenience. Various efficient oxidative methods require chromium (VI),[6a–d] or aqueous extraction.[6e–g] Many reagents are not selective for oximes in the presence of alkenes,[6d,e] or their selectivity patterns have not yet been explored.[6c,f–i] Two recent methods deoximate effectively while not reacting with alkenes.[6b,j] The present paper provides a convenient, high-yielding oxidative method using a non-toxic heterogeneous reagent in organic solvent that requires no aqueous workup.

The use of solid supported reagents in synthetic chemistry has become popular due to the altered reactivity, non-aqueous conditions and convenient product isolation they provide.[7] Studies by Lee and others have shown the fascinating chemistry of supported permanganate to be useful, varied and convenient. The heterogeneous reactions of sulfides, alkenes, unsaturated alcohols and benzylic hydrocarbons with $KMnO_4$ supported on $CuSO_4$ or Al_2O_3 are very different than the homogeneous, aqueous reactions. For example, some supported permanganate oxidations will not affect carbon–carbon double bonds,[8] but Singaram reported the selective oxidative cleavage of enamine double bonds,[9] and a convenient dehydrogenation[10] of 1,4-cyclohexadienes to aromatics using alumina supported potassium permanganate (ASPP).

We wish to report that ASPP deoximates ketoximes to the parent ketones cleanly and in good yield.[11] In addition, ASPP has shown an unexpected degree of selectivity for ketoximes in the presence of terminal alkenes. As a model substrate, we chose 4-t-butylcyclohexanone oxime (**1a**). **1a** (5 mmol) was dissolved in acetone (20 ml), cooled to 0°C, and alumina supported potassium permanganate (6 mmol $KMnO_4$, 2.0 g reagent) added in one portion with vigorous stirring. The reaction was monitored by gas chromatography (GC) until the starting material was consumed. In the case of **1a**, this was less than 5 minutes, and GC analysis indicated complete conversion to the ketone (**2a**). The supported oxidizing agent was removed by gravity filtration, and the filtrate condensed to give the crude, isolated product (82% yield, 99% pure, Eq. (1)).
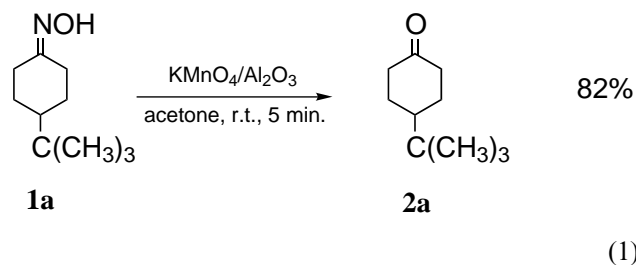
$$\textbf{1a} \xrightarrow[\text{acetone, r.t., 5 min.}]{KMnO_4/Al_2O_3} \textbf{2a} \quad 82\%$$

(1)

Encouraged by these results, we studied the reactions of a series of cyclohexanone oximes with increasing steric congestion near the carbonyl carbon. We found that as the steric demand of the oxime increased, the reaction time increased dramatically. This trend may be useful when considering various deoximation procedures, since the ASPP appears to prefer the least hindered oximes (Fig. 1).
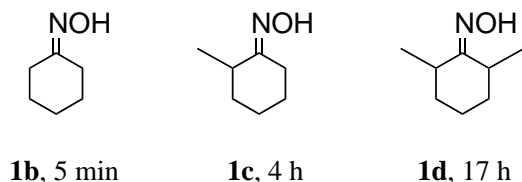

1b, 5 min   **1c**, 4 h   **1d**, 17 h

Figure 1. Reaction time required for deoximation of a series of cyclohexanone oximes.

During the oxidation of more hindered substrates the supernate turned bright green or blue. This color would persist after the reactions were complete for as long as 3 days. Since oximes and the product ketones give clear or light yellow solutions in acetone and methylene chloride, the colored solutions were attributed to side products such as intermediate manganese oxidation states. This was substantiated by the fact that a brown precipitate (MnO_2) formed as the color faded. GC analysis of the colored supernates revealed a complicated set of products not observed for less hindered substrate oxidations. No attempt was made to identify the side products.

To ensure the general utility of this reagent, a systematic study was conducted using 2-methylcyclohexanone oxime (**1c**) with the intention of eliminating side-reactions for more hindered substrates. Our first optimization experiments investigated the effects of changes in temperature, reagent addition and reagent preparation on product yield and purity. Running the reaction at 4°C tripled the reaction time, but did not change the product distribution or supernate color. Heating the heterogeneous reactions to reflux caused reduction of permanganate to occur more quickly, but produced much more intensely colored solutions and even more complicated reaction mixtures. Additional experiments showed that adding ASPP in several portions, and using reagent loaded with only 1 mmol $KMnO_4$/g reagent increased yields and decreased the concentration of side products. As a result, reactions from this point on were run using multiple additions of the 1 mmol $KMnO_4$/g ASPP reagent.
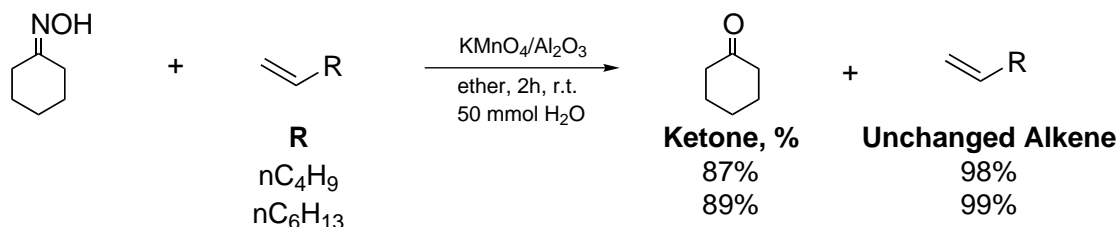
Next, the water content of ASPP was optimized. Lee and co-workers had utilized reagents containing up to 20% H_2O by weight. We prepared a reagent containing 1 mmol $KMnO_4$/g reagent that also contained 20% H_2O (w/w). When the model oxime was exposed to this reagent, exothermic reactions ensued providing the highest concentration of side-products observed, and the most intensely colored supernate. The addition of water had not improved results, so we sought to remove all water from the reaction. Since it is difficult to dry acetone, subsequent reactions were completed in anhydrous diethyl ether.[12] For this single example, a small amount of anhydrous $MgSO_4$ was added to the reaction mixture to minimize water concentration in solution. No reaction was observed even after 48 hours, and GC analysis showed no organic compounds in solution, not even starting material. We interpreted this to mean that the oxime was bound to the ASPP,[13] and that a minimal amount of H_2O was required for the oxidation to occur.[14] It was found that running the dry reaction as above but without $MgSO_4$ and with 50 mmol H_2O allowed practical reaction times with very little or no indication of by-products.

This optimized procedure proved to be quite general, working well for aliphatic, alicyclic and aromatic oximes.[15] Aliphatic examples **1e** and **1f** were oxidized to the corresponding 4-methyl-2-pentanone (**2e**) and 2-octanone (**2f**) in good yields. Finally, aromatic ketoxime **1g** was smoothly deoximated to give α-tetralone (**2g**) in 88% yield. No purification was required to isolate products in >95% purity. These results and the corresponding data are summarized in Table 1.

Table 1. Representative deoximations

Entry	Product	Yield	Reaction time (h)
1	4-*t*-Butylcyclohexanone (**2a**)[a]	85	2
2	Cyclohexanone (**2b**)	93	2
3	2-Methylcyclohexanone (**2c**)	86	3
4	2,5-Dimethylcyclohexanone (**2d**)	84	6
5	4-Methyl-2-pentanone (**2e**)	97	1
6	2-Octanone (**2f**)	91	1
7	α-Tetralone (**2g**)	88	2

[a] Note that the reaction times for unhindered oxime **1a** increased with the optimized procedure. Faster reaction times result when the amount of available water is increased, but this leads to side reactions in hindered substrates.

Figure 2. Selective deoximation in the presence of terminal alkenes.

In a control experiment, 4-methyl-2-pentanone oxime (**1e**) was stirred with dried alumina containing no permanganate under otherwise identical reaction conditions to address the possibility that alumina-catalyzed oxime hydrolysis might be occurring first, followed by an oxidation of hydroxylamine. The oxime was recovered unchanged (97% yield, 99.9% GC yield) indicating that ASPP is oxidizing the oxime itself, and not hydrolysis products. Next, we observed the competitive oxidation of cyclohexanone oxime in the presence of terminal alkenes. When equimolar solutions of cyclohexanone oxime and 1-hexene or 1-octene were treated with ASPP in the presence of an internal standard, GC analysis indicated that the oxime was exclusively oxidized to ketone (Fig. 2).

This method avoids the use of toxic reagents and an aqueous work-up—both environmental liabilities on the large scale. We hope this oxidative, non-aqueous method for selective deoximation of ketoximes in the presence of terminal alkenes will prove useful to organic chemists.

Acknowledgements

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11. A study in progress demonstrates that this reagent oxidizes aldehydes to acids, so deoximation of aldoximes is unlikely to be useful.
12. The reagent was still prepared from flame-dried alumina, and stored in a desiccator. No water was added to this reagent at any time.
13. To ensure that the $MgSO_4$ itself had not absorbed the oxime, 3 g $MgSO_4$, 50 ml diethyl ether and 10 mmol oxime were combined, stirred for 2 h, gravity filtered and analyzed. No oxime loss was observed.
14. The importance of water content and solvent in alumina supported permanganate reactions has been observed before, though not for this reaction: See, Lee, D. G.; Chen, T.; Wang, Z. *J. Org. Chem*. **1993**, *58*, 2918.
15. A representative procedure is as follows: alumina (neutral, 150 mesh) is dehydrated by heating to 300°C while stirring over a Bunsen burner for 15 minutes. After cooling in a desiccator, the alumina is ground together with potassium permanganate (1 mmol $KMnO_4$/g reagent) in a mortar and pestle until a homogeneous purple powder is obtained. Next, **1e** (2,5-dimethylcyclohexanone oxime, 5 mmol) was dissolved in diethyl ether (20 ml), cooled to 0°C, and alumina supported potassium permanganate (6 mmol $KMnO_4$, 6.0 g reagent) added in four portions with vigorous stirring. After the first 1.5 g portion was added, the mixture was allowed to stir for 5 minutes. Then, water (50 mmol, 0.9 ml) was added via pipette. The purple reagent was consumed and the brown color of MnO_2 appeared. The next portion of reagent was added when the $KMnO_4$ was consumed. To test this, a 1–2 drop sample of the reaction mixture was placed on a small piece of filter paper. If no purple color was observed when the sample spot was treated with two drops of water the next reagent portion was added. The reaction was monitored by GC until the starting material was consumed providing an 84% yield of ketone **2e**.