



## Enamine Oxidations. 2. Selective Oxidative Cleavage of $\beta,\beta$ -Disubstituted Enamines Using Alumina Supported Permanganate. Synthesis of One-Carbon Dehomologated Carbonyl Compounds from Enamines<sup>1</sup>

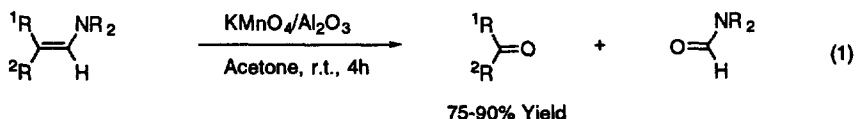
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**Abstract:** Treatment of  $\beta,\beta$ -disubstituted enamines with potassium permanganate supported on neutral alumina leads to a mild and selective oxidative cleavage reaction which produces ketones and formamides. The ketones can be isolated in high yield and purity by a simple workup procedure. The oxidizing agent is selective and preferentially oxidizes an enamine carbon-carbon double bond in the presence of a distal carbon-carbon double bond. Other functional groups unaffected by this reagent include nitriles, secondary alcohols, and alkynes allowing a wide range of potentially selective oxidations. © 1997, Elsevier Science Ltd. All rights reserved.

Over the last 15 years, the use of solid supports in synthetic chemistry has become more and more popular due to the altered reactivity, and convenient product isolation, they provide.<sup>2, 3</sup> Studies by Lee and coworkers have shown the fascinating chemistry of supported permanganate to be useful, varied and economical.<sup>4</sup> The heterogeneous reactions of sulfides, alkenes, unsaturated alcohols and benzylic carbons with potassium permanganate supported on copper sulfate or alumina ( $\text{Al}_2\text{O}_3$ ) are different than homogeneous, aqueous reactions.<sup>2</sup> For example, some supported permanganate reagents will not oxidize carbon-carbon double bonds.<sup>5</sup> However, other supported permanganate oxidations can be viewed as safer, less toxic and simpler alternatives for oxidative cleavage reactions, such as ozonolysis,<sup>6a</sup> and the osmium tetroxide / sodium periodate procedure.<sup>6a</sup> Photooxidation provides an excellent method for the dehomologation of some  $\alpha$ -substituted aldehydes to ketones, as well as the oxidative cleavage of a few selected enamines.<sup>6c</sup> As part of our study of enamines, we were interested in the oxidative cleavage of enamine double bonds. Recently, we reported that the oxidative cleavage of enamines using chromic acid provides a route to the dehomologation of carbonyl compounds.<sup>1</sup> Although this method avoids some extreme reaction conditions, it still requires the use of a suspected carcinogen. Additionally, in the case of exocyclic enamine **1e**, chromic acid oxidation provided the cleavage product, cyclohexanone, in low yield. This prompted us to investigate the use of supported permanganate with enamines. In this communication we report the first oxidative cleavage of enamines by an alumina supported potassium permanganate reagent.

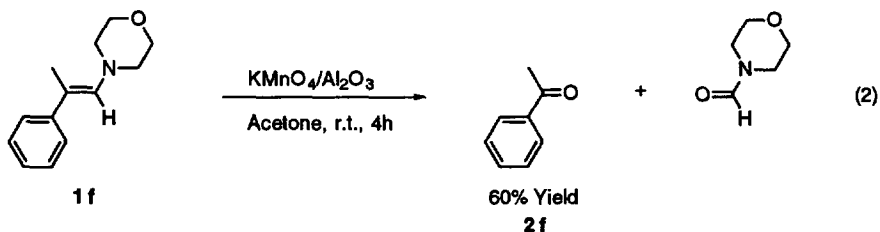
Enamine **1f** was chosen as a model substrate in order to take advantage of the simple structure and easy isolation of the anticipated product, acetophenone (**2f**). We then set out to determine the necessary conditions for an oxidative cleavage reaction. A systematic variation of the substituents on the amine nitrogen as well as the enamine  $\beta$ -carbon then served to probe the limits of the reaction (eq. 1).



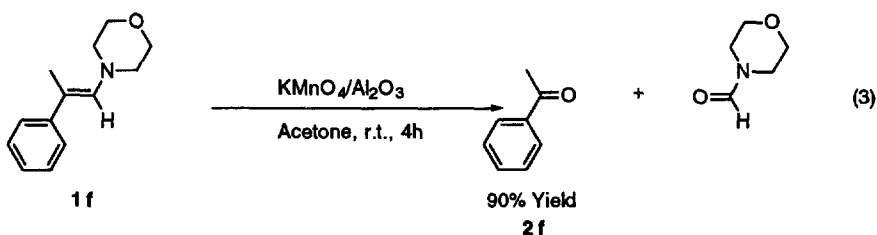
$\text{R}^1 = \text{R}^2 = \text{alkyl, aryl}$

$\text{NR}_2 = \text{morpholine, piperidine, N-ethylaniline, N-methyl-N-benzylamine}$

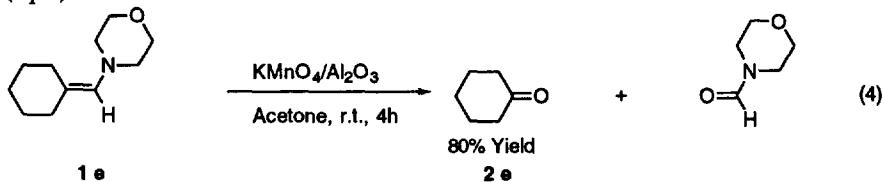
In our initial reactions, we found that aromatic enamine **1f** was oxidatively cleaved by the alumina supported permanganate to give acetophenone (**2f**) in a reproducible 60% yield (eq. 2).



Control experiments using the same enamine and unmodified  $\text{KMnO}_4$  powder, in acetone, gave acetophenone in less than 50% yield. In each of these experiments, hydrolysis of the starting enamine was the competing reaction. Not unexpectedly, we found that the mass of water initially present in the alumina, or added to the reagent, affected the product yields dramatically. Since water had a detrimental effect on this oxidation reaction, only flame-dried alumina was used in the preparation of the supported potassium permanganate reagent. We found that a reagent containing 3 mmol of  $\text{KMnO}_4$  per gram of total reagent gave the best product yields. In addition, spectral grade acetone was found to be superior to hexane and ether as the reaction solvent (eq. 3).



Using this procedure, aliphatic enamines **1a-d** give 80-91% yields of the corresponding ketones. Easily hydrolysable **1e** was oxidized to cyclohexanone in a dramatically improved yield compared to chromic acid oxidation (eq. 4).<sup>1</sup>



Oxidative cleavage of aryl enamines **1f** and **1g** under the same conditions provides the corresponding ketones in 75-90% yield.

This heterogeneous permanganate oxidation is a simple procedure. A thirty mmol batch of the reagent is prepared by combining  $\text{KMnO}_4$  (30 mmol, 4.75g, finely ground) and alumina ( $\text{Al}_2\text{O}_3$ , neutral, 5.75g) in a mortar and pestle and grinding together until a fine, homogeneous, purple powder is obtained (5-10 minutes). The enamine (3 mmols) is then dissolved in acetone, and the  $\text{KMnO}_4 / \text{Al}_2\text{O}_3$  powder (1.33 g supported reagent, 4 mmols  $\text{KMnO}_4$ ) added. After four hours of vigorous stirring, the reaction mixture is filtered and the acetone filtrate condensed. The residue is taken up into ether, washed with dilute hydrochloric acid, dried ( $\text{MgSO}_4$ ), and the ether evaporated to give the crude material. The results are summarized in **Table 1**.

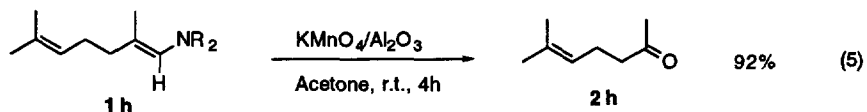
**Table 1.** Alumina Supported Permanganate Conversion of  $\beta,\beta$ -Disubstituted Enamines to Ketones

enamine		ketone <sup>a</sup>		yield, %	bp, °C (Torr) <sup>d</sup>
2-methyl-1-(4-morpholino)-1-pentene	(1a)	2-pentanone	(2a)	83 <sup>c</sup>	
2-ethyl-1-(4-morpholino)-1-butene	(1b)	3-pentanone	(2b)	80 <sup>c</sup>	
2-methyl-1-(4-morpholino)-1-undecene	(1c)	2-undecanone	(2c)	84 <sup>b</sup>	50-51°C (0.1)
3-(4-isopropyl)-phenyl-2-methyl-1-(4-morpholino)-1-propene	(1d)	1-(4-isopropyl)phenyl-2-propanone	(2d)	91 <sup>b</sup>	69-70°C (0.1)
4-(cyclohexylidene-methyl)-morpholine	(1e)	cyclohexanone	(2e)	80 <sup>c</sup>	
1-(4-morpholino)-2-phenylpropene	(1f)	acetophenone	(2f)	90 <sup>b</sup>	35-36°C (0.1)
1-(4-morpholino)-2,2-diphenylethene	(1g)	benzophenone	(2g)	75 <sup>b</sup>	125°C (0.1)

<sup>a</sup>All enamines and ketones fully characterized by 250 MHz  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR. <sup>b</sup>Isolated, distilled yields. <sup>c</sup>G.C. yields.

<sup>d</sup>Boiling points are uncorrected.

Encouraged by these results, we investigated the chemoselectivity of the alumina supported potassium permanganate. We were gratified to find that this reagent allows the selective oxidation of enamine carbon-carbon double bonds in the presence of distal alkenes. For example, dienamine **1h** was oxidized to enone **2h** in 92% yield (eq. 5)



In addition, the supported permanganate reagent does not react with either cyclohexanol or 1-octyne even after 3 h at 25°. This reagent is also unreactive towards heptanenitrile and benzonitrile, even after 8 h. Consequently, this reagent should give selective cleavage of the enamine double bond in the presence of functional groups such as nitriles, secondary alcohols, and even alkynes. The oxidation is not just limited to morpholino enamines, and works equally well with enamines derived from piperidine, *N*-ethylaniline and *N*-methyl-*N*-benzylamine.

In conclusion, the supported permanganate oxidation of  $\beta,\beta$ -disubstituted enamines is an economical, convenient method for the dehomologation of  $\alpha,\alpha$ -disubstituted aldehydes to ketones. The procedure utilizes inexpensive reagents, is easily carried out, and the workup is simple. This method avoids the use of chromic acid, which should allow its wider application in organic synthesis. Surprisingly, the strongly oxidizing potassium permanganate does not rapidly oxidize alkynes when it is supported on dry alumina. We are actively studying the oxidation of a wide variety of enamines, enols, and other functional groups, including difunctional compounds.

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