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A Facile Dehomologation of α-Substituted Aldehydes to the Corresponding Ketones

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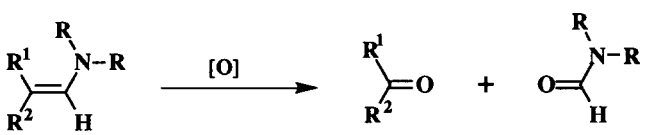
Abstract *A systematic study has been completed demonstrating the utility and scope of the potassium dichromate-mediated oxidative cleavage of enamines. Among the methods studied, the biphasic, chromic acid-diethyl ether conditions gave the best results and prevented over-oxidation of the carbonyl products. This method is general for β, β –disubstituted enamines, such as (1E)-1-(4-morpholino)-2-phenyl-2-methyl-1-propene, and gave the corresponding dehomologated ketones in good yield in one hour at 25 °C.*

As part of our study of the hydroboration of enamines, we were interested in the direct oxidation of enamines.[1] We were fascinated by a recent publication detailing the sodium periodate oxidation of aryl enamines leading to the oxidative cleavage of the enamine double bond.[2] Further investigation revealed that this type of reaction has been known for over forty years and that a number of different reagents have been developed to achieve the transformation (eq. 1).



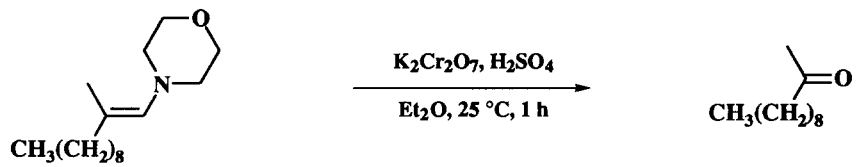
(1)

Among these are sodium periodate,[2] sodium dichromate in acid,[3] *meta*-chloroperbenzoic acid,[4] nitrous acid,[5] and molecular oxygen with copper ion systems.[6]

However, the reactions of most of these reagents have not been studied systematically, and the dichromate examples studied were limited to enamines derived from steroids.[3] Consequently, we undertook a systematic study of the sodium dichromate oxidation of enamines to check the generality of the reaction.

First, we applied the dichromate-acetic acid conditions[3a,b] to several different types of enamines. We found that β, β-disubstituted enamines reacted more cleanly than α, β-disubstituted terminal and cyclic enamines, giving the corresponding ketone in good yields. Unfortunately, we found that the product was contaminated with hydrolysis product and required rigorous washing with sodium hydroxide to remove excess acetic acid. We opted to replace these conditions with the standard Jones oxidation procedure, but obtained mainly the hydrolyzed starting material (aldehyde) or the corresponding carboxylic acid. We speculated that the use of a biphasic aqueous chromic acid-diethyl ether system would facilitate the oxidation while suppressing the hydrolysis of the enamine. The enamine substrate is probably made water soluble by formation of a chromic acid ester intermediate. The water insoluble ketone product is subsequently returned to, and protected from over-oxidation by, the organic layer after the oxidation is completed.[7] Accordingly, we added one equivalent of a 0.4 M potassium dichromate / 0.4 M sulfuric acid aqueous solution to 10 mmoles of 1-(4-morpholino)-2-methyl-1-

undecene dissolved in 50 mL of diethyl ether (Et_2O) and stirred vigorously for one hour (eq. 2).



(2)

The workup was now easier for the oxidation of this and other enamine substrates, but many of the yields were still unacceptably low. We then studied the effect of concentration and stoichiometry on the yield of this reaction. The results are summarized in **Table 1**.

Table 1. The Effect of Dichromate Concentration and Stoichiometry on Ketone Yield in the Oxidative Cleavage of 1-(4-Morpholino)-2-methyl-1-undecene

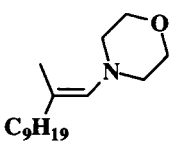
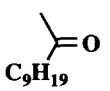
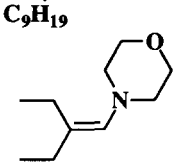
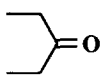
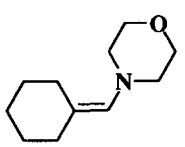
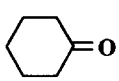
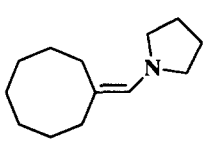
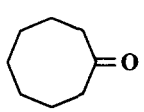
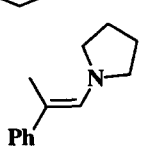
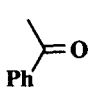
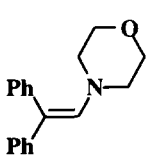
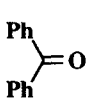
$K_2Cr_2O_7$ / H_2SO_4 concentration[a]	equivalents[b]	% yield[c,d]
0.33 M	1	52
0.40 M	1	78
0.66 M	1	60
0.40 M	2	83

[a]In each case $[K_2Cr_2O_7] = [H_2SO_4]$. [b]Molar equivalents of $K_2Cr_2O_7$ per enamine. [c]Product purity was determined by 250 MHz ^1H NMR and ^{13}C NMR. [d]Isolated yield.

We found that reducing the concentration of the oxidizing agent to 0.33 M reduced the yield of ketone. Increasing the concentration to 0.66 M also reduced the yield. Apparently the 0.40 M solution is the optimal balance between the conditions which are too acidic and the conditions which are only weakly oxidative, thus preventing the desired reaction and favoring hydrolysis. With this knowledge in hand, we adjusted the stoichiometry and found that two equivalents gave a slight increase in the yield of 2-undecanone. Consequently, we used two equivalents of the oxidizing agent to oxidize a series of enamines with straight chain, alicyclic, and aromatic substituents. The results are summarized in **Table 2**.[8] We found that two equivalents of the 0.40 M $K_2Cr_2O_7$ / H_2SO_4 solution gave consistently good yields of 2-undecanone and 3-pentanone from the corresponding enamines (**Table 2**, entries 1 and 2). The cyclic enamines were oxidized to the corresponding cyclic ketones (**Table 2**, entries 3 and 4), and substituting aromatic groups at the β-position gave acetophenone

and benzophenone (**Table 2**, entries 5 and 6).

Table 2. Bi-phasic Oxidation of Enamines with Acidified Potassium Dichromate: The Use of Two Equivalents of the 0.40 M $K_2Cr_2O_7/H_2SO_4$ Reagent.

entry	enamine	product[b]	yield[c]	bp°C (Torr) [d]
1			83	79-80 (0.25)
2			75	71-72 (144)
3			37	85-86 (100)
4			73	84-85 (0.03)
5			75	51-53 (0.01)
6			88	108-109 (1.0)

[a]The reagent is 0.40 M in both $K_2Cr_2O_7$ and H_2SO_4. [b]Product purity determined by 250 MHz ^1H NMR and ^{13}C NMR. [c]Isolated yield. [d]Boiling points are uncorrected.

We have demonstrated the scope and limitations of the dichromate, biphasic method of oxidizing aldehyde enamines. We found that the dehomologated ketones were produced in good yields with very little hydrolysis for almost every β,β-disubstituted enamine we investigated. This method, in conjunction with the facile conversion

of aldehydes to enamines,[9] constitutes a convenient strategy for dehomologation of an α–disubstituted aldehyde to the corresponding ketone.

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(8) The following procedure is representative: A 100 mL serum vial equipped with a magnetic stir bar was charged at 25 °C with (*1E*)-1-(4-morpholino)-2-phenyl-2-methyl-1-propene (1.9 g, 10 mmol) and diethyl ether (50 mL). The reaction mixture was stirred until homogeneous (5 minutes) and 0.40 M $K_2Cr_2O_7$ / H_2SO_4 (50 mL, 20 mmol) was added by pipet (ten minutes) while stirring vigorously. The reaction was allowed to stir at 25 °C for 1 h. The reaction mixture was extracted with Et_2O (2 X 50 mL) and the combined organic portions washed with saturated $NaHCO_3$ (2 X 25 mL) until neutral to litmus and dried over $MgSO_4$. The solvent was removed *in vacuo* (12 torr) to give a 3:1 mixture of acetophenone and the aldehyde hydrolysis product. One distillation gave pure acetophenone as a colorless liquid (0.9g, 75%, b.p. 51-53 °C, .01 torr).

(9) Fisher, G. B.; Lee, L.; Klettke, F. W. *Synth. Commun.* **1994**, *24*, 1541.

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