

$\alpha$ -HYDROXYLATION OF KETONES:  
OSMIUM TETROXIDE/N-METHYLMORPHOLINE-N-OXIDE  
OXIDATION OF SILYL ENOL ETHERS

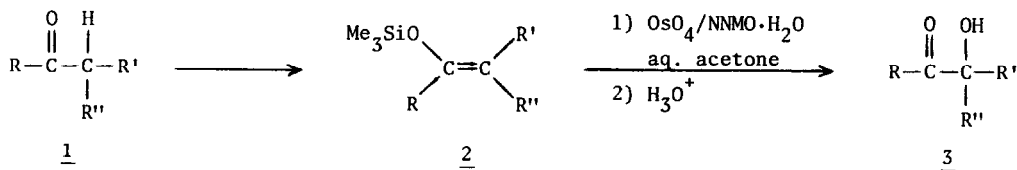
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**Abstract:** Osmium tetroxide/N-methylmorpholine-N-oxide oxidation of silyl enol ethers, derived from ketones with either kinetic or thermodynamic regiochemical control, produces  $\alpha$ -ketols in good to excellent yields.

The search for means to introduce hydroxyl functionality adjacent to carbonyl has led to development of some elegant methods, including oxidation of enolates by a molybdenum peroxide reagent<sup>1</sup> or by molecular oxygen<sup>2</sup> and oxidation of trimethylsilyl enol ethers by peracid<sup>3</sup> or by photosensitized oxygenation.<sup>4</sup> However, in the application of such methods results are sensitive to ketone structure and the formation of byproducts often is observed. Since ketone hydroxylation is required in a number of important natural product syntheses, such as anthracyclines, corticosteroids, and prostaglandins, in addition to a supposed byssinotic agent of interest in this laboratory, other effective means have been sought. Because oxidation of the desired, relatively sensitive  $\alpha$ -ketols is one of the problems, it seemed reasonable that improved yields for oxidative formation of this functionality might be obtained using an agent of attenuated strength acting on a precursor of enhanced susceptibility to oxidation. Furthermore, use of such a ketone-derived precursor could permit regiochemical control of ultimate hydroxylation.

The contrasting regiochemistry of silyl enol ether formation via kinetically and thermodynamically derived enolates,<sup>5</sup> the ease and nearly quantitative yields with which these silyl enol ethers may be prepared, and the enhanced reactivity of silyloxyalkenes toward electrophilic species<sup>5,6</sup> make such substances attractive intermediates for  $\alpha$ -hydroxylation methodology.<sup>3,4</sup> An especially mild, oxidative procedure for diol formation from olefins employing osmium tetroxide together with N-methylmorpholine-N-oxide (monohydrate, NMMO·H<sub>2</sub>O) as stoichiometric oxidant has been reported.<sup>7</sup> These reagents permit the desired transformation of silyl enol ethers into  $\alpha$ -ketols in good to excellent yields.

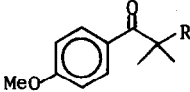
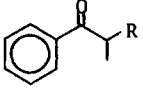
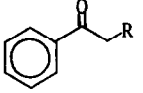
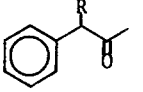
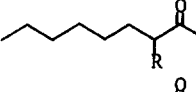

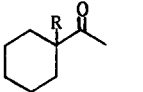
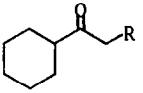
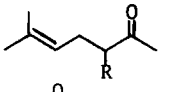
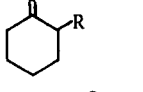
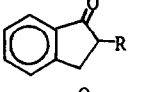
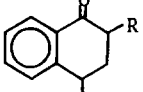
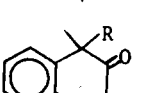
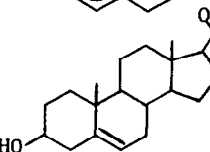


The requisite trimethylsilyl enol ethers can be generated from ketones by a variety of methods, three of which were employed in this investigation: enolate generation using lithium diisopropylamide (LDA) in THF (to form regioselectively the kinetic enolate)<sup>5</sup> or KH in THF, with subsequent addition of trimethylsilyl chloride; alternatively, the thermodynamically more stable enol ether could be obtained with high selectivity using trimethylsilyl iodide (TMSI) and hexamethyldisilazane (HMDS) in methylene chloride.<sup>8</sup> These intermediates generally were not purified before oxidation.

Treatment of these silyl enol ethers in aqueous acetone with a catalytic amount of osmium tetroxide together with one equivalent of NMMO·H<sub>2</sub>O at -10 to 25°C generally accomplished smooth oxidation which was allowed to proceed until disappearance of the enol ether as determined by tlc (commonly, 1-10 h). Subsequent workup afforded α-ketols in yields which generally ranged from 60-95%. The Table contains results (two step, overall yields)<sup>9</sup> obtained from ketones 4-17, chosen to reveal capabilities of the method for ketones of varying substitution, the potential for regiochemical control, and the compatibility with other olefinic functionality. Generally, hydroxylation proceeds best at methine and methylene positions, and results for methyl functionalization compare favorably with those for other methods.<sup>1-3</sup> As demonstrated by hydroxylation reactions of ketones 8-12, by proper choice of method for enol ether formation it is possible to functionalize methyl ketones regioselectively at either methyl or a more highly substituted position.<sup>10</sup> As expected, remote olefinic functionality is unaffected under the reaction conditions (e.g., 12 and 17). A noteworthy example is hydroxylation of pregnenolone, 17, which contains both olefinic and hydroxy functionality remote from the carbonyl group. Regiospecific hydroxylation of C-21 could be accomplished in 59% overall yield.<sup>11</sup>

Preparation of α-hydroxypropiophenone (5, R = OH) illustrates a typical procedure: A solution containing 412 mg (2.0 mmol) of the trimethylsilyl enol ether (2, R = Ph, R' = Me, R'' = H) in 3 mL of acetone was added at -5°C to a mixture containing 0.04 mmol of OsO<sub>4</sub> (added as a solution in 0.91 mL of *t*-butyl alcohol),<sup>12</sup> 284 mg (2.1 mmol) of NMMO·H<sub>2</sub>O, and 4 mL of H<sub>2</sub>O in 9 mL of acetone. The resulting mixture was stirred at 0°C for 3 h, then allowed to warm to 25°C and stirred an additional 6 h. Sodium hydrosulfite (0.35 g) and Florisil (1.34 g) were added, the suspension was stirred and filtered to remove osmium-containing material, the filtrate was neutralized to pH 7 with 1 N H<sub>2</sub>SO<sub>4</sub>, and the acetone was removed *in vacuo*. After further acidification to pH 2 and saturation with NaCl, the mixture was extracted with ethyl acetate to give a solution which was dried (MgSO<sub>4</sub>) and concentrated to afford 562 mg of material. Chromatographic purification (silica gel, 40% ethyl acetate/hexane) gave 293 mg (1.96 mmol, 98%) of 2-hydroxy-1-phenyl-1-propanone. Variations of this procedure may improve yields. For example, for 1-indanone (14), addition of the ketone to the oxidant was preferable. More importantly, the ratio of oxidation to hydrolysis, which can be a significantly competing process (e.g., examples 10, 14, 16), can be increased by using *tert*-butyl alcohol as solvent with pyridine as catalyst.<sup>13</sup> Thus, in aqueous acetone the relative amounts of α-ketol:ketone were ca 1:5 for ketone 16, while in *tert*-butyl alcohol (plus 0.1 mL pyridine and 0.1 mL H<sub>2</sub>O/mmol ketone) this ratio was increased to 25:1.

In addition to α-hydroxylation of ketones, this oxidative method permits access to α-ketols from silyl enol ethers obtained by methods<sup>5,14</sup> which do not involve ketone precursors. As well, this approach should be applicable to α-hydroxylation of other carbonyl functionalities.

Starting Ketone (R = H)	Method of Enol Ether Formation	Yields <sup>a</sup> of Product $\alpha$ -Ketol (R = OH)
<u>4</u> 	KH	94%
<u>5</u> 	KH or TMSI/HMDS	98%
<u>6</u> 	KH	70%
<u>7</u> 	LDA	91%
<u>8</u> 	TMSI/HMDS	69%
<u>9</u> 	LDA	54%
<u>10</u> 	TMSI/HMDS	68% (77%) <sup>b</sup>
<u>11</u> 	LDA	59%
<u>12</u> 	TMSI/HMDS	57%
<u>13</u> 	TMSI/HMDS	89%
<u>14</u> 	TMSI/HMDS	58% (73%) <sup>b,c</sup>
<u>15</u> 	LDA	60%
<u>16</u> 	TMSI/HMDS	54% <sup>c</sup>
<u>17</u> 	LDA	59% <sup>d</sup>

a) Two-step yields (based on ketone), after purification. b) Values in parentheses: yields based on recovered ketone. c) Special conditions used; see text. d) See note 11.

References and Notes

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9. All yields are after purification. In all cases, spectral and physical data of the  $\alpha$ -ketols were in accord with literature data.
10. For examples 8 and 10, the TMSI/HMDS method permitted ca. 92:8 selectivity for functionalization at the more highly substituted position. Contaminating hydroxymethyl product was easily removed during final purification.
11. For pregnenolone (17), 3 molar equivalents of LDA in dioxane, followed by an excess of trimethylsilyl chloride and triethylamine, were used to prepare the bis(trimethylsilyl) derivative. This compound was oxidized in the usual manner; the C-3 trimethylsilyl ether was hydrolyzed during the normal workup procedure.
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Acknowledgment: Financial support by Cotton Incorporated is appreciated.

(Received in USA 11 August 1980)