PART II

CHAPTER VII

"THE USE OF MIXED LIGAND Co(II) COMPLEX IN DEOXIMATION OF OXIMES TO CARBONYL COMPOUNDS"
THE USE OF MIXED LIGAND Co(II) COMPLEX IN DEOXIMATION OF OXIMES TO CARBONYL COMPOUNDS

Deoximation reaction: A review

Introduction:

Oximes are nitrogen derivatives of aldehydes and ketones and are crystalline compounds. They are preferred for purification and characterization of carbonyl compounds as well as useful as protecting group. They play an important role as selectively α-activating group in multistep synthesis. Furthermore, their synthesis from non-carbonyl compounds provides an alternative pathway to carbonyl compounds. Regeneration of carbonyl compound from the corresponding oximes, popularly known as deoximation, is a very important reaction. As such there has been increasing interest in the development of mild, fast and environmentally benign methods of deoximation. So far a good number of methods based on hydrolytic, reductive and oxidative reactions have been developed.

Hydrolytic methods: Hydrolysis of oximes to produce the parent carbonyl is best observed in acidic condition amongst various acidic, basic or neutral conditions(Scheme VII.1). It is the oldest method of deoximation. It removes the hydroxylamine from the equilibrium.

\[
\text{R}_1\text{NOH} \xrightarrow{\text{H}_2\text{O/H}^+} \text{R}_1\text{=alkyl, aryl} \quad \text{R}_2=\text{H, alkyl, aryl}
\]

Scheme VII.1

Acid hydrolysis has been carried out with various acids such as oxalic acid, acetic acid, p-tolunesulfonic acid, Phthalic anhydride-water, hydrobromic acid, sulfuric acid which have been used in aqueous solution or another cosolvent in relation to the solubility of the oxime. Some catalytic salts such as cupric sulfate pentahydrate, cupric nitrate supported on silica gel, iron(III)ammonium sulfate to dilute $\text{H}_2\text{SO}_4$, Clayen, Dowex-50 have also
resulted in complete conversion. Recently, surfactant promoted I\textsubscript{2} catalyzed cleavage of the >C=N bond of oximes in water under neutral condition has been exploited\textsuperscript{17} (Scheme VII.2).

![Scheme VII.2](image)

**Exchange reaction with other carbonyl compounds:** The exchange reaction with other carbonyl compounds has been an extensively applied method. Formaldehyde and acetone have been applied for such reactions (Scheme VII.3).

![Scheme VII.3](image)

Although use of acetone involves non-acidic reaction medium, simple work-up and inexpensive reagents, it gives very low yield. Two other acids used in such reaction are Pyruvic acid\textsuperscript{18} and levulinic acid\textsuperscript{19} have also been used.

**Reductive methods:**

Although many types of reductive reagents such as hydrogen and heterogenous catalysts, metal carboxyls, metals and acids, hydrides, sulfurated reagents were used for deoximation, transition metal ions such as titanium(II), titanium(III), chromium(II), vanadium(II) and molybdenum(III) were more extensively used because of their convenient redox potential\textsuperscript{20}. These reductive reagents cause the fission of the oxime N-O linkage to give an imine which undergoes rapid hydrolysis to the carbonyl compounds (Scheme VII.4).

![Scheme VII.4](image)
Raney nickel in the presence of boric acid and acetone has been used for reductive transformation of ketoximes to ketones\textsuperscript{21}. Oximes were also found to be cleaved by addition of zinc dust to a solution of molybdenyl chloride in THF\textsuperscript{22}. HMPA (10\%) (Hexamethylphosphoramide) in THF\textsuperscript{23} can be applied for conversion of ketoximes to ketones in presence of LiAlH\textsubscript{4} (Scheme VII.5).

![Chemical structure](image)

\textbf{(Scheme VII.5)}

Among the metal carbonyls, iron as well as cobalt and molybdenum have shown comparable efficiency. The reaction of diiron noncarbonyl or iron pentacarbonyl with ketoximes under photoirradiation or thermal conditions afforded the corresponding ketones in modest to good yield\textsuperscript{24}. Molybdenum hexacarbonyl and Dicobaltoctacarbonyl [Co(CO)\textsubscript{8}] were found to be good reagents for easy generation of carbonyl functionalities from their oxime derivatives\textsuperscript{25}. Titanium chloride/ sodium iodide (TiCl\textsubscript{4}/NaI)\textsuperscript{26} system generating low-valent titanium (LVT) is a mild, efficient and selective reagent for reductive cleavage of oximes (Scheme VII.6). The reaction is very rapid using acetonitrile as solvent and a 1:2:2 ratio of oxime/sodium iodide/titanium tetrachloride.

![Chemical structure](image)

\textbf{(Scheme VII.6)}
Reductive deoximation of oximes can also be accomplished in good yields by treatment of a tetrahydrofuran solution of oxime with aqueous vanadium chloride\(^{27}\) at room temperature under a nitrogen atmosphere with the advantage of an easy work-up which is practically free of side products (Scheme VII.7).

(Scheme VII.7)

Sulfurated reagents sodium dithionate and sodium hydrogen sulfite has also been used for deoximation. Aqueous sodium dithionite\((\text{Na}_2\text{S}_2\text{O}_4)^{28}\) at room temperature either alone or in the presence of sodium hydrogen carbonate or sodium acetate results the parent carbonyl compound after addition of an acid. The reaction has its own importance as sodium dithionite is inexpensive; reaction condition is mild, rapid generation of carbonyl compound and above all the reaction is applicable to both aldoximes and ketoximes.

**Oxidative methods:**

The methods based on oxidative reaction make use of several oxidizing agents. These include chromium reagents such as pyridinium chlorochromate\(^{29}\), pyridinium chlorochromate-\(\text{H}_2\text{O}_2\)^{30}, trimethylammonium chlorochromate\(^{31}\), trimethylsilyl chlorochromate\(^{32}\), chlorotrimethylsilane-(chromium)\(^{33}\), bis(trimethylsilyl) chromate\(^{34}\), unsupported \(\text{CrO}_3\)^{35}, polymer supported\(^{36}\) as well as silica supported \(\text{CrO}_3\)^{37}; supported reagents like clayfen\(^{38}\), ammonium persulfate-silica gel\(^{39}\), periodic acid\(^{40}\), dinitrogen tetroxide\(^{41}\), dimethyldioxirane\(^{42}\); different manganese salts like manganese triacetate\(^{43}\), bis(pyridine)silver permanganate\(^{44}\), manganese dioxide\(^{45}\); Bismuth(III) nitrate\(^{46}\), iron(III) porphyrins and phosphotungstic acid\(^{47}\); t-butylhydroperoxide\(^{48}\), N-haloamines\(^{49}\); and halogens.
and halogenated compounds like Dess-Martin periodinane (DMP)\textsuperscript{50} and O-iodoxybenzoic acid\textsuperscript{51}. Among the chromium based oxidizing agents, chromium(VI) ion, such as dichromate and chromate, are known to be optimum oxidizing agents which have given good results in the mild oxidative deoximation of ketoximes, but not in deoximation of aldoximes, as these reactions afford overoxidised products. The best results were obtained when the counter ion was a pyridinium ion. Halochromates such as pyridinium or quinolinium fluorochromate and pyridinium chlororomate have found extensive use as oxidizing agents. Other halochromates are dimethylammonium and methylammonium chlorochromate absorbed on alumina, which are easily accessible and stable reagents. Another useful reagent is 2,6-dicarboxypyridinium chlorochromate(2,6-DCPCC). A noteworthy advantage of the reagent is the exclusive oxidation of oximes irrespective of the presence of semicarbazones and phenylhydrazones.

A combination of pyridinium dichromate and t-butylhydroperoxide has been found to provide excellent reagents for the new, highly selective deblocking procedure of ketoximes. Recently it has been reported that quinolium chlorochromate give excellent results in deoximation. It was observed that electron withdrawing substituent on aromatic ring also gave good yields and no over oxidation was observed. Clay supported ammonium nitrate\textsuperscript{38} is a useful addition to the array of deoximation reactions(Scheme VII.8). The reaction is carried out in DCM and work up is done simply by extraction and separation of the reagent by filtration.

\begin{equation}
\begin{array}{c}
\text{Clayfen} \\
\text{MW}
\end{array}
\end{equation}

(Scheme VII.8)

Similarly, silica supported ammonium persulfate\textsuperscript{39} is an environmentally benign and safe oxidant in deoximation(Scheme VII.9). The use of recyclable silica gel support and general applicability of this reaction to a variety of aldoximes and ketoximes under solvent free conditions are other attractive features of this protocol.
Metallic as well as organic permanganates have been used fruitfully in various deoximation reactions (Scheme VII.9).

\[
\begin{align*}
R_1 & \text{N-OH} \quad (\text{NH})_2S_2O_8\text{-silica} \\
\text{MW} & \quad \rightarrow \\
R_1 & \text{O} \\
\text{(Scheme VII.9)}
\end{align*}
\]

Metallic as well as organic permanganates have been used fruitfully in various deoximation reactions (Scheme VII.10).

\[
\begin{align*}
R_1 & \text{N-OH} \quad \text{Y MnO}_4 \\
\text{YMnO}_4 & \quad \rightarrow \\
R_1 & \text{O} \\
\text{CH}_3\text{CN/H}_2\text{O} \quad & \quad \text{Y=K\textsuperscript{+}, Ba\textsuperscript{2+}, CTA\textsuperscript{+}, BPS\textsuperscript{+}, B(2,2\textsuperscript{-}BP)Cu\textsuperscript{2+}} \\
\text{(Scheme VII.10)}
\end{align*}
\]

e.g. bis(pyridine)silver permanganate\textsuperscript{44} operates in dichloromethane, benzene or acetone at room temperature. Potassium permanganate supported on zeolites has been found to be an excellent reagent for deoximation. Commercially available activated MnO\textsubscript{2}\textsuperscript{45} in aprotic solvents such as hexane or DCM at room temperature has been used because of simple procedure, high yield from both aldoximes and ketoximes as well as wide applicability to highly functionalized oximes including acyclic galactose pentaacetate oxime.

Very recently, MnO\textsubscript{2} has been used for the regeneration of 4\textsuperscript{-}amino[1,1\textsuperscript{-}biphenyl]-2-carbaldehyde\textsuperscript{53} (Scheme VII.11).

\[
\begin{align*}
\text{NOH} & \quad \text{MnO}_2 \\
\text{NH}_2 & \quad \text{Benzene} \\
\text{NH}_2 & \quad \text{O} \\
\text{(Scheme VII.11)}
\end{align*}
\]

Demir et al\textsuperscript{43} reported manganese(III) acetate a further possible reagent to employ under mild reaction conditions (Scheme VII.12).
Application of bismuth(III) nitrate pentahydrate as a relatively non-toxic, air-sensitive and inexpensive reagent which, coupled with relatively non-toxic solvent system (acetone-water, 9:1) constitutes of an attractive alternative to the exciting routes for deprotection of oximes. Recently, microwave assisted silica supported bismuth trichloride in THF also have been reported.

Water soluble iron(III) porphyrins and phosphotungstic acid in an ionic liquid were found to be effective catalyst for the H$_2$O$_2$ mediated oxidation of the >C=NOH bond in N-hydroxyarginine and other oximes (Scheme VII.13). These system serves as biomimetic models of nitric oxide synthase (NOS) and the catalyst immobilized in an ionic liquid can be easily recycled and reused.

Readily available tert-butyl hydroperoxide (TBHP) (70%) has been found to be an efficient and selective reagent for the mild oxidative cleavage of the C=N of oximes under neutral conditions (Scheme VII.14).

Because of their low price and versatility halogenated compounds have been successfully used in reactions of deoximation and given good results. Deoximation using the Dess-Martin periodinane (DMP) [1,1,1-triacetoxy-1,1-
dihydro-1,2-benziodoxol-3(1H)-one\] (Scheme VII.15) and 1-hydroxy-1,2-
benziodoxol-3(1H)-one-1-oxide(IBX) are, in particular, important because

(i) mild nature of DMP and IBX
(ii) reaction occurs at room temperature with rapid rate and easy work up
procedure
(iii) high yield.

Photosensitized deprotection of oximes by platinum(II)terpyridyl acetylide
complex has been reported recently\(^{52}\). The reaction proceeds via singlet
oxygen\(^{1}\) mechanism. This singlet oxygen reacts with aldoximes and
ketoximes to produce their corresponding carbonyl compounds(Scheme VII.16).

Herein is reported a facile method of deoximation to the parent carbonyl
compounds using the reported decomposition of \(\text{H}_2\text{O}_2\) with mixed ligand cobalt(II)
complexes. The procedure of deoximation is simple and cost effective and yields
of the regenerated carbonyl compound are high. This method of deoximation is applicable to both the aldoximes and the ketoximes. The mixed ligand cobalt(II) complex were prepared by the reaction of 1:1:1 proportion of cobalt(II) chloride hexahydrate, glycine and 8-hydroxyquinoline according to a reported procedure. It is noteworthy that, unlike other methods of deoximation, the major drawback of overoxidation of the generated aldehydes to the carboxylic acids and formation of by products by the oxidation of solvents was not observed. Furthermore, acid and base sensitive groups remained unaffected and finally solvent oxidation products were not detected. The oxidation is possibly carried out by molecular oxygen which is generated in situ by the decomposition of $H_2O_2$ by the Co(II) catalyst. The catalyst could be prepared from easily and cheap starting compounds. Further, the greatest advantage is that the cobalt catalyst could be recycled and reused many times without any manipulation. Very little reduction of activity of the catalyst was observed. The reaction is shown in scheme VII.17 and the observations are summarized in Table VII.1

![Chemical reaction](image)

(Scheme VII.17)

**Experimental:**

All reagents and solvents were purified by methods reported in literature. Melting points were recorded in an apparatus from Scientific devices, India, Type MP-D, in open capillaries and $^1H$ NMR spectra were recorded in Varian 400 MHz NMR. Several oximes were prepared by using the procedure reported in literature and characterized by comparing their melting points with those reported in literature and also by comparing the $^1H$ NMR spectra, IR spectra with authentic samples.
Chapter VII

General procedure:

Preparation of mixed ligand cobalt(II) complex: The complex was prepared by using 8-hydroxyquinoline as the primary ligand and glycine as the secondary ligand. To a blue coloured ethanolic solution (10 ml) of cobalt(II) chloride hexahydrate (0.237g, 1mmol) was added an ethanolic (10ml) solution of 8-hydroxyquinoline (0.147g, 1mmol). The mixture turned green after stirring and keeping in a boiling water bath for 10 min. To this was added an aqueous solution of glycine (1mmol). The mixture was then heated in a water bath for another 10 min. The mixture was then cooled and the solid filtered, washed with ice cold water followed by washing with aqueous ethanol. The complex thus prepared was dried in vacuum.

Deoximation:

In a triple necked round bottom flask (50ml) equipped with a condenser and a pressure equalizing funnel a solution of the substrate oxime (1mmol) in 10 ml methanol was taken. The mixed ligand cobalt(II) catalyst (0.0252, 0.1mmol) was added to this solution and refluxed for varying period of time (2-3hrs). During reflux 15ml of 30% H₂O₂ was added to the solution under reflux in three lots of equal volume. After the addition of H₂O₂ was complete, the mixture was refluxed for further 30 min. The reaction mixture was allowed to cool to room temperature and methanol was removed. The solid obtained was extracted with ether and on evaporation of the solvent gave the desired product. The crude product was purified by column chromatography using ethylacetate-petroleum ether (40-60) in varying proportions as the eluent. Reduced pressure removal of the eluent gave the generated carbonyl compound.

The results are summarized in table I. The aromatic aldehydes obtained as the product did not require elaborate techniques for their identification. Comparison of melting point and IR spectra to those of authentic sample were adequate enough for their identification.
Chapter VII

Table I • Deoximation using mixed ligand Co(II) Complex and hydrogen peroxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction time (hrs)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate" /></td>
<td><img src="image2" alt="Product" /></td>
<td>2.5</td>
<td>79</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate" /></td>
<td><img src="image4" alt="Product" /></td>
<td>2</td>
<td>90</td>
<td>42-43</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate" /></td>
<td><img src="image6" alt="Product" /></td>
<td>2</td>
<td>88</td>
<td>106</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate" /></td>
<td><img src="image8" alt="Product" /></td>
<td>2</td>
<td>91</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate" /></td>
<td><img src="image10" alt="Product" /></td>
<td>2.5</td>
<td>78</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Substrate" /></td>
<td><img src="image12" alt="Product" /></td>
<td>2</td>
<td>82</td>
<td>116</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Substrate" /></td>
<td><img src="image14" alt="Product" /></td>
<td>2.5</td>
<td>85</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Substrate" /></td>
<td><img src="image16" alt="Product" /></td>
<td>1.5</td>
<td>72</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17" alt="Substrate" /></td>
<td><img src="image18" alt="Product" /></td>
<td>2</td>
<td>86</td>
<td>77-80</td>
</tr>
<tr>
<td>10</td>
<td><img src="image19" alt="Substrate" /></td>
<td><img src="image20" alt="Product" /></td>
<td>2.5</td>
<td>83</td>
<td>79</td>
</tr>
</tbody>
</table>

i) reaction solvent: MeOH  ii) Yield % calculated on the basis of solid products obtained
Some spectral characteristics of the regenerated carbonyl compounds from Oximes:

Product 1: Benzophenone: UV: $\lambda_{\text{max}}$(95% EtOH) 282.6 nm, IR(KBr): $\text{cm}^{-1}$ 1710.5 (C=O), $^1\text{H}$ NMR(300 MHz, CDCl$_3$): $\delta$ 7.2 (broad, 10H)

Product 2: 2-nitrobenzaldehyde: UV: $\lambda_{\text{max}}$(95% EtOH) 277 nm, IR(KBr): $\text{cm}^{-1}$ 1730 (C=O); 1552, 1332(-NO$_2$), $^1\text{H}$ NMR(300 MHz, CDCl$_3$): $\delta$ 9.1 (s, 1H), 8.1 (broad, 4H)

Product 3: 4-nitrobenzaldehyde: UV: $\lambda_{\text{max}}$(95% EtOH) 285.5 nm, IR(KBr): $\text{cm}^{-1}$ 1715.6 (C=O); 1595.6, 1279.1 (-NO$_2$), $^1\text{H}$ NMR(300 MHz, CDCl$_3$): $\delta$ 9.1 (s,1H), 7.7-7.9 (broad, 4H)

Product 4: 3-nitrobenzaldehyde: UV: $\lambda_{\text{max}}$(95% EtOH) 295.6 nm
IR(KBr): $\text{cm}^{-1}$ 1713.5 (C=O); 1515.4, 1320.3(-NO$_2$), $^1\text{H}$ NMR(300 MHz, CDCl$_3$): $\delta$ 8.7 (s,1H), 7.3-7.8 (d, 4H)

Product 5: 4-chlorobenzaldehyde: UV: $\lambda_{\text{max}}$(95% EtOH) 285.7 nm
IR(KBr): $\text{cm}^{-1}$ 1700 (C=O), $^1\text{H}$ NMR(300 MHz, CDCl$_3$): $\delta$ 9.2 (s,1H), 7.3-7.7 (d, 4H)

Product 6: 4-hydroxybenzaldehyde: UV: $\lambda_{\text{max}}$(95% EtOH) 280.8 nm
IR(KBr): $\text{cm}^{-1}$ 1675.8 (C=O), 3490(-OH) $^1\text{H}$ NMR(300 MHz, CDCl$_3$): $\delta$ 9.8 (s,1H), 6.9 (s, 1H), 7.4-7.8 (m, 4H)

Product 7: 2,6-dichlorobenzaldehyde: UV: $\lambda_{\text{max}}$(95% EtOH) 235.5 nm
IR(KBr): $\text{cm}^{-1}$ 1680.4 (C=O), $^1\text{H}$ NMR(300 MHz, CDCl$_3$): $\delta$ 9.5 (s,1H), 7.9 (m, 3H)

Product 8: Methyl-2-naphthylketone: UV: $\lambda_{\text{max}}$(95% EtOH) 312.8 nm
IR(KBr): $\text{cm}^{-1}$ 1670 (C=O), $^1\text{H}$ NMR(300 MHz, CDCl$_3$): $\delta$ 7.5 (m,7H), 2.2 (s, 3H)

Product 10: Vanillin: UV: $\lambda_{\text{max}}$(95% EtOH) 295.6 nm, IR(KBr): $\text{cm}^{-1}$ 1666.3 (C=O), 3186 (-OH), $^1\text{H}$ NMR(300 MHz, CDCl$_3$): $\delta$ 9.8 (s,1H), 7.4 (s,2H), 7.05 (s,1H), 6.6 (s, 1H), 3.9 (s,3H)

Conclusion:
The experiments carried out establishes the fact that the decomposition of H$_2$O$_2$ by mixed ligand cobalt(II) complexes can be conveniently used as a procedure for easy oxidative deoximation.
UV-VISIBLE SPECTRUM OF
"Mixed ligand Co(II) complex"
IR SPECTRUM OF "Vanillin"
IR SPECTRUM OF
"4-chlorobenzaldehyde"
References:

20. Ho, T. L. Synthesis 1979, 1