PART C

Oxidation of alcohols into carbonyl compounds under reflux
IC. 1. OXIDATION OF ALCOHOLS

The oxidation of alcohols plays an important role in organic synthesis as it is a fundamental synthetic transformation. Development of new oxidative processes continue to draw attention in spite of the availability of numerous oxidizing reagents.[1] A wide variety of reagents have been employed previously for this reaction.[2-4] The reported oxidizing reagents are often used in stoichiometric amounts and are either hazardous or toxic. Hence, in terms of economical and environmental concern, catalytic oxidation processes which involves high conversions without side products, inexpensive and non-toxic reagents which work and mild conditions with high chemoselectivity, tolerance to other functional groups and environmental oxidants are extremely valuable. In the field of synthetic natural products, the steps frequently involve the conversions of compounds with multiple oxygen containing functional groups at different oxidation states. Hence, it often becomes necessary to selectively oxidize a single secondary or primary alcoholic group within the same molecule. This problem has been continuously challenging the synthetic organic chemists in the areas of carbohydrates and steroid synthesis and many of the selective oxidations are originated from these fields. One of the best method to encounter the individual alcohol group is by selective protection or deprotection. Selective oxidizing agents which can distinguish primary alcohols from secondary alcohols are desirable alternatives to the use of protecting groups in the synthesis. Most of the reagents which are commonly used oxidize secondary alcohols at slightly faster rates than primary alcohols due to intermolecular competition experiments and regioselective oxidations of diols and polyhydroxylated compounds.[5]


Oxidation of alcohols to carbonyl compounds under reflux
The introduction of metallic reagents on solid supports have solved some of the problems associated with toxicity and provides an attractive alternative to the conventional oxidation reactions in view of the selectivity and ease of manipulation. Several MW-assisted oxidative protocols have been developed [6–9] using an array of supported reagents applicable to both alcohols and sulfides (Fig. IC.1).[10]

![Chemical Diagram](attachment:chemistry-diagram.png)

**Fig. IC.1.**

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*Oxidation of alcohols to carbonyl compounds under reflux*
IC. 2. SOME INTERESTING AND USEFUL OXIDATION REACTIONS

A rapid oxidation of primary and secondary alcohols using catalytic amounts of TEMPO and Yb(OTf)₃ in combination with a stoichiometric amount of iodosylbenzene afforded carbonyl compounds in excellent yields without over-oxidation. Oxidation of primary alcohols in the presence of secondary alcohols proceeded with good selectivity (Scheme IC.1).[11]

\[
\begin{align*}
\text{OH} & \quad \xrightarrow{1.3 \ \text{eq. PhIO}} \\
R - R' & \quad \xrightarrow{5 \ \text{mol} \% \ \text{TEMPO}} \\
R & \quad \xrightarrow{2 \ \text{mol} \% \ \text{Yb(OTf)}_3} \\
\text{CH}_2\text{Cl}_2, \text{r.t., 0.25-7 h} & \quad \xrightarrow{\text{O}} \\
R - R' & \quad \xrightarrow{R = \text{alkyl, benzyl, allyl}} \\
\end{align*}
\]

Scheme IC.1.

A novel, mild oxidation system for the synthesis of aldehydes and ketones using oxone, catalytic amount of TEMPO and a quaternary ammonium salt is reported which is especially successful for the synthesis of ketones. This procedure even tolerates silyl protective groups which are normally cleaved in the presence of oxone (Scheme IC.2).[12]

\[
\begin{align*}
\text{OH} & \quad \xrightarrow{1 \ \text{mol} \% \ \text{TEMPO}} \\
R & \quad \xrightarrow{4 \ \text{mol} \% \ n-\text{Bu}_2\text{NBr}} \\
\text{CH}_2\text{Cl}_2, \text{r.t., > 12 h} & \quad \xrightarrow{2.2 \ \text{eq. Oxone}} \\
\end{align*}
\]

Scheme IC.2.

The combination of TEMPO and CAN is used for the aerobic oxidation of benzylic and allylic alcohols into their corresponding carbonyl compounds. This method is superior to other methods due to its relatively short reaction times and excellent yields (Scheme IC.3).[13]


Oxidation of alcohols to carbonyl compounds under reflux
Scheme IC.3.

Keggin-type heteropoly acids revealed high catalytic activity for swift and selective oxidation of various hydroxy functionalities to the corresponding carbonyl groups using ferric nitrate as an oxidant under mild and solvent-free conditions (Scheme IC.4).[14]

Scheme IC.4.

A new, green, mild and inexpensive system, I$_2$-KI-K$_2$CO$_3$-H$_2$O, selectively oxidized alcohols to aldehydes and ketones under anaerobic condition in water at 90 °C with excellent yields (Scheme IC.5).[15]

Scheme IC.5.

A chemoselective and efficient procedure allows the conversion of benzylic and allylic alcohols into the corresponding carbonyl compounds with sodium nitrate as oxidant in the presence of 3-methylimidazolinium hydrogensulfate (Scheme IC.6).[16]

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Scheme IC.6.

Benzyl alcohols and benzyl TBDMS ethers were efficiently oxidized to the corresponding carbonyl compounds in high yield with periodic acid catalyzed by CrO₃ at low temperature (-78 °C). The oxidation procedure was highly functional group tolerant and very selective for the TBDMS group over the TBDPS group (Scheme IC.7).[17]

Scheme IC.7.

The oxidation of primary and secondary alcohols by sodium percarbonate in the presence of catalytic amounts of both molybdenyl acetylacetone and Adogen 464 to give high yields of the corresponding carbonyl compounds is available in the literature (Scheme IC.8).[18]

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*Oxidation of alcohols to carbonyl compounds under reflux*
**Scheme IC.8.**

An efficient protocol for the oxidation of alcohols to aldehyde and ketones under atmospheric oxygen with catalytic amount of V$_2$O$_5$ in toluene at 100°C is reported. Secondary alcohols are chemoselectively converted into ketones in the presence of primary hydroxy groups (Scheme IC.9).[19]

**Scheme IC.9.**

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*Oxidation of alcohols to carbonyl compounds under reflux*
IC. 3. PRESENT WORK: OXIDATION OF ALCOHOLS INTO CARBONYL COMPOUNDS USING Ni(NO₃)₂·6H₂O/p-TsA/WATER UNDER REFLUX

IC. 3.1. INTRODUCTION

Oxidation of alcohols into corresponding carbonyl compounds is an important transformation in organic synthesis. In particular, the controlled oxidation of primary alcohols to aldehydes, without forming over-oxidized product is really a challenging task. In this part we are presenting the use of Ni(NO₃)₂·6H₂O/p-TsA/water system at 60–90 °C for the rapid oxidation of primary alcohols to aldehydes and secondary alcohols into ketones. The process is mild and inexpensive; the yields are high and the reactions go to completion within 15–20 min (Schemes IC.10 and Schemes IC.11).

![Chemical Reaction](attachment:image.png)

Scheme IC.10.

![Chemical Reaction](attachment:image.png)

Scheme IC.11.

IC. 3.2. RESULTS AND DISCUSSION

In order to develop a new and effective catalytic system for the oxidation of alcohols without forming over oxidized product, different catalytic systems were tried. As metal nitrates are known to oxidize alcohols,[20,21] To start with nickel nitrate was selected for the purpose; however, with nickel nitrate alone only a trace amount of oxidized product was obtained even after several hours.[21]


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We then used water as a solvent, the yield went upto 30 %, which was also not appreciable. Then catalytic addition of acidic catalyst increased the yield of the desired product to 85 %. The results of these studies are presented in the Table IC.1.

From Table IC.1, it is clear that, the oxidation of alcohols using Ni(NO₃)₂·6H₂O/p-TsA/water system under reflux is efficient and gives high yield of the products in short duration.

Table IC.1: A comparative study on the oxidation of benzylalcohol to benzaldehyde in presence of different reagent systems at 60 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent System</th>
<th>Reaction time (min) at 60 °C</th>
<th>Product⁹</th>
<th>Yield (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(NO₃)₂·6H₂O/water</td>
<td>80</td>
<td>Aldehyde/acid</td>
<td>30/50</td>
</tr>
<tr>
<td>2</td>
<td>Ni(NO₃)₂·6H₂O/p-TsA/water</td>
<td>40</td>
<td>Aldehyde</td>
<td>82</td>
</tr>
</tbody>
</table>

ᵃ Characterized by IR and GC-mass spectral analysis and by comparison with authentic samples.ᵇ Isolated yields.

In order to find the suitability of the Ni(NO₃)₂·6H₂O/p-TsA/water system for the oxidation of alcohols, different substituted alcohols were selected and the oxidation was carried out under reflux condition. The results of this study are presented in Table IC.2. From Table IC.2, it is clear that, primary alcohols give aldehydes and secodary alcohols give ketones in high yields.

Table IC.2: Oxidation of alcohols to aldehydes and ketones in the presence of Ni(NO₃)₂·6H₂O/p-TsA/water under reflux.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction time (min)</th>
<th>Product⁹</th>
<th>Yield (%)ᵈ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzyl alcohol</td>
<td>30</td>
<td>Benzaldehyde</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>Anisyl alcohol</td>
<td>25</td>
<td>Anisaldehyde</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>3-Nitrobenzyl alcohol</td>
<td>35</td>
<td>3-Nitrobenzaldehyde</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>2-Chlorobenzyl alcohol</td>
<td>40</td>
<td>2-Chlorobenzaldehyde</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>Furfuryl alcohol</td>
<td>20</td>
<td>Furfuraldehyde</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>Cyclohexanol</td>
<td>40</td>
<td>Cyclohexanone</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>Cyclopentanol</td>
<td>40</td>
<td>Cyclopantanone</td>
<td>83</td>
</tr>
</tbody>
</table>

⁹ Oxidation of alcohols to carbonyl compounds under reflux

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IC. 3.3. EXPERIMENTAL

Anisyl alcohol, 3-nitrobenzyl alcohol, 2-chlorobenzyl alcohol and furfuryl alcohol were prepared by the reduction of respective aldehydes. All the other reagents used were commercially available. The products were characterized by IR and GC-mass spectral analysis. All the reactions were studied using SHIMATZU GC-MS QP 5050 instrument.

IC. 3.4. GENERAL PROCEDURE FOR THE OXIDATION OF BENZYL ALCOHOL

A mixture of benzyl alcohol (1.08 g, 10 mmol), Ni(NO₃)₂·6H₂O (2.908 g, 10 mmol), p-TsA (0.475 g, 2.5 mmol) and water (5 mL) were heated at 60 °C for 20 minutes. After completion of the reaction (monitored by TLC), the product was taken into diethyl ether (10 mL), the organic matter was washed with saturated sodium bicarbonate solution (2.5 mL), water (5 mL) and then dried over anhydrous sodium sulphate. Pure benzaldehyde was obtained after the removal of solvent under vacuum. The product was characterized by IR, GC-mass spectral analysis and compared with the authentic sample.

IC. 3.5. MECHANISM

A plausible mechanism for the oxidation of alcohols to carbonyl compounds is envisaged in Scheme IC.12. Alcohols are expected to react with nickel nitrate which on activation with p-TsA is expected to give intermediate A, subsequent loss on nitrous acid gives the intermediate B. Regeneration of the catalyst by the attack of sulfonate ion affords the required carbonyl compound.

\[
\begin{align*}
\text{Scheme IC.12.} \\
\text{Oxidation of alcohols to carbonyl compounds under reflux}
\end{align*}
\]
IC. 3.6. CONCLUSIONS

In conclusion, an easy approach to the oxidation of primary alcohols into aldehydes and secondary alcohols into ketones using Ni(NO$_3$)$_2$·6H$_2$O/$p$-TsA/water system under reflux condition is developed. The reaction is facile, involves simple workup, uses readily available and inexpensive chemicals and gives high yield of the products in short duration. Hence, this procedure could be an useful alternative to the currently available methods.

IC. 3.7. SPECTRAL DATA

Benzaldehyde (Table IC.2, entry 1) IR (KBr) $\nu$ = 3086, 3066, 3028, 2860, 2825, 2730, 2696, 1980, 1915, 1900, 1828, 1700, 1664, 1580, 1456, 1390, 1311, 1288, 1204, 1010, 924, 725, 660, 610, 467 cm$^{-1}$; MS (70 ev), $m/z$: 106 [M$^+$]

Anisaldehyde (Table IC.2, entry 2) IR (KBr) $\nu$ = 3080, 3050, 3028, 2960, 2935, 2900, 2841, 2825, 2800, 2720, 1700, 1684, 1520, 1460, 1442, 1425, 1390, 1300, 1258, 1180, 1100, 1020, 855, 820, 640, 632, 610, 590, 515 cm$^{-1}$; MS (70 ev), $m/z$: 122 [M$^+$]

3-Nitrobenzaldehyde (Table IC.2, entry 3) IR (KBr) $\nu$ = 3070, 3052, 3020, 2963, 2940, 2910, 2845, 2820, 2715, 1710, 1681, 1520, 1448, 1350, 1302, 1250, 1178, 1020, 850, 812, 640, 632, 610, 590, 515 cm$^{-1}$; MS (70 ev), $m/z$: 151 [M$^+$]

2-Chlorobenzaldehyde (Table IC.2, entry 4) IR (KBr) $\nu$ = 3082, 3071, 3028, 2869, 2824, 2733, 2690, 1982, 1910, 1818, 1700, 1664, 1560, 1450, 1390, 1301, 1289, 1200, 1012, 914, 785, 660, 610, 540, 467 cm$^{-1}$; MS (70 ev), $m/z$: 140 [M$^+$]

Furfuraldehyde (Table IC.2, entry 5) IR (KBr) $\nu$ = 3062, 2848, 2820, 2731, 1982, 1910, 1829, 1702, 1676, 1530, 1450, 1300, 1210, 1012, 914, 540, 467 cm$^{-1}$; MS (70 ev), $m/z$: 96 [M$^+$]

Cyclohexanone (Table IC.2, entry 6) IR (KBr) $\nu$ = 3610, 3510, 3400, 2943, 2860, 2678, 2643, 2611, 1878, 1800, 1765, 1711, 1652, 1625, 1423, 1400, 1346, 1311, 1257, 1070, 999, 905, 840, 650, 490 cm$^{-1}$; MS (70 ev), $m/z$: 98 [M$^+$]

Cyclopentanone (Table IC.2, entry 7) IR (KBr) $\nu$ = 3622, 3530, 3380, 2842, 2876, 2701, 2641, 2609, 2599, 1870, 1812, 1763, 1688, 1650, 1612, 1420, 1398, 1346, 1302, 1255, 1188, 1067, 1000, 915, 868, 653, 576, 499 cm$^{-1}$; MS (70 ev), $m/z$: 84 [M$^+$]

Oxidation of alcohols to carbonyl compounds under reflux
Cycloheptanone (Table IC.2, entry 8) IR (KBr) $\nu = 3590, 3500, 3424, 3333, 2848, 2866, 2670, 2643, 2611, 2577, 1870, 1803, 1793, 1765, 1700, 1655, 1625, 1420, 1388, 1346, 1311, 1247, 1048, 1000, 915, 888, 650, 523, 490 $ cm$^{-1}$; MS (70 ev), $m/z$: 112 [M$^+$]

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Oxidation of alcohols to carbonyl compounds under reflux
Fig. IC.1.  *Mass spectrum of benzaldehyde* (Table 1C.2, entry 1)

Fig. IC.2.  *Mass spectrum of anisaldehyde* (Table 1C.2, entry 2)

*Oxidation of alcohols to carbonyl compounds under reflux*
Fig. IC.3.  Mass spectrum of 3-nitrobenzaldehyde (Table 1C.2, entry 3)

Fig. IC.4.  Mass spectrum of cyclohexanone (Table 1C.2, entry 6)

Oxidation of alcohols to carbonyl compounds under reflux