REGENERATION OF CARBONYL COMPOUNDS FROM THEIR DERIVATIVES

Introduction:
The use of blocking functions in organic synthesis developed for nearly 100 years but use of blocking agents complicates the entire synthetic plan since it requires at least two additional steps. At the same time, environmental and economic considerations have created interest in both academic and industrial research in designing synthetic procedures that are clean, selective, high yielding and easy to manipulate. An extensive application of heterogeneous catalysis and modified phase transfer catalyst in synthetic chemistry can help to achieve new selective reactions, to lower the waste production and finally to render more attractive the synthetic process from both environmental and also the economic point of view, in agreement with the parameters of "ideal synthesis". Due to great interest in protecting group chemistry, many books\textsuperscript{1,2} and reviews\textsuperscript{3,4} have been published on this topic. Several reviews have touched upon more specialized field such as enzymatic protecting group technique\textsuperscript{5} and protecting groups in solid phase organic synthesis\textsuperscript{6}.

In this review, only the protection and deprotection of carbonyl group is considered. The electrophilic nature of the carbonyl group is a dominant feature of its extensive chemistry. One of the major challenging problems during many multistep syntheses is how to protect a carbonyl group from nucleophilic attack. The protection of aldehydes and ketones have been served by a relatively small repertoire of protecting groups and out of these, acetals, thiacetals, oxathiolanes, 1,1-diacetates and nitrogenous derivatives have been proposed. Cyclic acetals of keto steroids were cleaved by using $\text{H}_2\text{SO}_4$\textsuperscript{7} or Cu(II) sulphate\textsuperscript{8} supported on silica. NaY zeolites promoted the cleavage of acetals in the presence of nitrobenzene at room temperature.

In this chapter, experimental procedure are reported for the regeneration of the parent carbonyl compounds, mainly the aromatic aldehydes from 1,1-diacetates, 2-arylbenzimidazoles and 2-arylbenzoxazole by the oxidative method using a
hydrated medium, by using H₂O₂ with mixed ligand Co(II) complexes and by the use of tetra-n-alkylammonium bromate. It may be well mentioned that regeneration of the parent carbonyl from the 1,1-diacetate derivatives have already been carried out by several deprotecting reagents and a short review is mentioned.

**Deprotection of 1,1-diacetate—a review:**
The borontriiodide-N,N-diethylaniline complex generated in situ from boron-N,N-diethylaniline and iodine cleaves ethers and regenerates the aldehydes from the corresponding geminal diacetate derivatives⁹ (Scheme IX.1)

![Scheme IX.1](image)

Benzaldehyde diacetates were selectively converted to the corresponding benzaldehydes using Ceric ammonium nitrate (CAN) coated on silica in DCM as a solvent¹⁰ (Scheme IX.2)

![Scheme IX.2](image)

Potassium phenoxide were found to cleave various geminal diketals and regenerate aldehydes¹¹ (Scheme IX.3).

![Scheme IX.3](image)
Selective deprotection of benzaldehyde diacetate on neutral alumina surface is possible through gentle heating, microwave irradiation as well as conventional methods\textsuperscript{12} (Scheme IX.4).

\[
\begin{align*}
\text{RCH(OAc)}_2 & \xrightarrow{\text{neutral Al}_2\text{O}_3} \text{RCHO} \\
\text{CH}_2\text{Cl}_2, \text{rt} & \\
\end{align*}
\]

Scheme IX.4

Treatment of acylals from benzaldehyde cyclohexane carboxylate with water in the presence of scandium triflate gave deprotected aldehyde\textsuperscript{13} (Scheme IX.5).

\[
\begin{align*}
\text{OAc} & \\
\text{R} & \text{OAc} \\
\xrightarrow{20\text{mol}\% \text{Sc(OTf)}_3} & \xrightarrow{\text{MeNO}_2, \text{10min}, \text{H}_2\text{O}} \\
\end{align*}
\]

Scheme IX.5

A variety of 1,1-diacetate are easily and efficiently deprotected in the presence of catalytic amount of Bismuth(III) chloride affording the corresponding aldehydes\textsuperscript{14} (Scheme IX.6).

\[
\begin{align*}
\text{RCH(OAc)}_2 & \xrightarrow{\text{BiCl}_3/\text{CHCl}_3} \text{RCHO} \\
\text{reflux} & \\
\end{align*}
\]

Scheme IX.6

Gem diacetates are selectively deprotected to the corresponding aldehydes by CB\textsubscript{4} in refluxing acetonitrile\textsuperscript{15} (Scheme IX.7).

\[
\begin{align*}
\text{RCH(OAc)}_2 & \xrightarrow{\text{CB}_4-\text{acetonitrile}} \text{RCHO} \\
\text{reflux} & \\
\end{align*}
\]

Scheme IX.7

The reaction of acylals derived from aldehydes with water in the presence of 10% Indium(III) chloride gave the parent aldehyde in a short reaction time\textsuperscript{16} (Scheme IX.8).

\[
\begin{align*}
\text{RCH(OAc)}_2 & \xrightarrow{\text{InCl}_3} \text{RCHO} \\
\text{H}_2\text{O}, \text{rt} & \\
\end{align*}
\]

Scheme IX.8
Rapid cleavage of geminal diacetates with Zirconium chloride (ZrCl₄) in methanol at room temperature and with sulfated zirconia in distilled acetonitrile at 60°C is also observed¹⁸ (Scheme IX.9).

![Scheme IX.9](image)

In this study a method for deprotection of 1,1-diacetate derived from several aromatic aldehydes using a solid acid already reported in chapter II have been discussed. The deprotection of the diacetates to the corresponding aldehydes has been carried out in a hydrated medium using a mixture of aqueous formic acid in presence of a surfactant SDS in different proportion. The procedure reported assumes importance due to the fact that deprotection have been carried out in aqueous medium hence environment friendly. The yield of the parent aldehyde, however was moderate. The process of regeneration is shown in Scheme IX.10 given below

![Scheme IX.10](image)
The details of the experiments carried out are given in the experimental section.

Experimental:
All chemicals used were procured from Merck Inc. (India).

The substrate 1,1-diacetate of several aldehydes were prepared by using a solid acid as detailed in Chapter II. These 1,1-diacetates were converted back to the parent aromatic aldehydes according to the procedure given below.

**Deprotection in hydrated media using surfactants:**
In a typical procedure, a mixture of the 1,1-diacetate (1 mmol) in 10ml of 20% aqueous SDS and aqueous HCOOH in varying proportions was taken in a 100ml round bottomed flask and refluxed for varying period of time as shown in table IX.1. After completion of the reaction as monitored by TLC, the reaction mixture was poured into water and the resultant aldehyde precipitated out. The aldehyde were purified by recrystallization. The yield of the parent aromatic aldehyde varied from 40-90% as shown in the table IX.1
Table IX.1-experimental details of regeneration of aldehydes from diacetates

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction condition (% SDS,% HCOOH)</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate" /></td>
<td><img src="image2" alt="Product" /></td>
<td>20, 20</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate" /></td>
<td><img src="image4" alt="Product" /></td>
<td>20, 20</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate" /></td>
<td><img src="image6" alt="Product" /></td>
<td>20, 30</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate" /></td>
<td><img src="image8" alt="Product" /></td>
<td>20, 50</td>
<td>5.5</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate" /></td>
<td><img src="image10" alt="Product" /></td>
<td>20, 60</td>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Substrate" /></td>
<td><img src="image12" alt="Product" /></td>
<td>20, 30</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Substrate" /></td>
<td><img src="image14" alt="Product" /></td>
<td>20, 80</td>
<td>7</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Substrate" /></td>
<td><img src="image16" alt="Product" /></td>
<td>20, 40</td>
<td>7.5</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17" alt="Substrate" /></td>
<td><img src="image18" alt="Product" /></td>
<td>20, 40</td>
<td>8</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td><img src="image19" alt="Substrate" /></td>
<td><img src="image20" alt="Product" /></td>
<td>20, 80</td>
<td>9</td>
<td>40</td>
</tr>
</tbody>
</table>
Chapter IX

Protection of Carbonyl group by the formation of heterocyclic ring and their conversion to the parent aldehydes:
The carbonyl group have also been protected by their conversion to heterocycles and notable among them are the formation of 1,3-dioxolanes. A series of 2-substituted and 2,2-disubstituted 1,3-benzodioxolanes have been synthesized using montmorillonite KSF or K10\textsuperscript{10} (Scheme IX.11).

![Scheme IX.11](image)

Y-zeolite HSZ-360 has been demonstrated to be effective in the formation of 1,3-dioxolanes. There are several other methods reported for protection of the carbonyl by the formation of the 1,3-dioxolanes and notable among the procedures are the following

Zirconium sulfophenylphosphonate has been investigated for the preparation of 1,3-dioxolanes from several carbonyl compounds. The reaction in general occurs and in satisfactory to good yield\textsuperscript{20} (Scheme IX.12).

![Scheme IX.12](image)

The regeneration of carbonyl compounds from their cyclic acetals is generally performed under acidic conditions and for this purpose, different heterogeneous catalysts have been proposed. Among all the deprotecting reagents NaY zeolite...
was found to be an effective water tolerant catalyst in the selective deprotection of these acetals. A mild and easy regeneration of the carbonyl compound from their benzylic dioxolanes has been carried out by Habibi et al under potassium dodecatungstocobaltate trihydrate. The method seems to be unaffected by the bulkiness of the starting acetals\textsuperscript{21}.

Another method of protecting the carbonyl via the formation of a heterocycle is the conversion to dithioacetals. These compounds are obtained by protic or Lewis acid catalysed condensation of carbonyl compounds with thiols or by transdithioacetalization has been proposed by Patney based on the use of Fe(III) chloride dispersed on silica gel\textsuperscript{22}. Production of dithianes and dithiolanes could be achieved in the presence of montmorillonite KSF clay without solvents. Kumar et al reported the use of Y zeolites to prepare thioacetales of aldehydes and ketones\textsuperscript{23}.

Commercially available acidic resin such as Amberlyst 15 and dowex 50W have been employed for dethioacetalization via equilibrium exchange with aqueous acetone/paraformaldehyde\textsuperscript{24,25}(Scheme IX.13).

Layered zirconium sulfophenyl phosphonate has also been utilized with similar good results for the mild hydrolysis of 1,1-dithiolanes and 1,3-dithianes to the parent carbonyl compounds\textsuperscript{26}. 1,3-oxathiolanes constitute an important class of compounds that are more stable than the corresponding O,O-acetales under acidic conditions and compared to S,S-acetales are more easily deprotected. Natural clay promoted the efficient chemoselective production of a variety of oxathiolanes by a dithiolane exchange reaction from aldehydes or ketones with 2,2-dimethyl-1,3-oxathiolanes(Scheme IX.14).
Chapter IX

Amberlyst 15 can also be utilized for the conversion of carbonyl compounds to 1,3-oxathiolanes\textsuperscript{27}. Following this procedure, a wide range of carbonyl compounds can be efficiently transformed to their corresponding 1,3-oxathiolanes (Scheme IX.15).

Carbonyl compounds were regenerated from the parent 1,3-oxathiolanes via an equilibrium exchange with glyoxalic acid and amberlyst 15 under solvent free condition at room temperature under microwave irradiation\textsuperscript{28} (Scheme IX.16).

Generation of the parent aldehyde from 2-arylbenzimidazoles: In this study, 2-arylbenzimidazoles were prepared by the reaction of an aromatic aldehyde with o-phenylenediamine using a solid acid as a catalyst as discussed in chapter III of this thesis. The benzimidazoles were characterized by spectroscopic as well as the physical methods. These 2-arylbenzimidazoles were converted to the parent carbonyl compound by an oxidative method using H\textsubscript{2}O\textsubscript{2} in the presence of a
mixed ligand cobalt(II) complex. The transformation is shown in the following scheme (Scheme IX.17)

![Scheme IX.17](image)

The ease with which the 2-arylbenzimidazoles were converted to the parent carbonyl compound indicates that formation of the 2-arylbenzimidazoles can also be a good method for the protection of the carbonyl compound. The reagent used for the conversion may be useful when the substrate has acid sensitive groups as the deprotection is carried out under neutral conditions. The details of the experimental procedure carried out as under.

**Procedure of conversion of 2-arylbenzimidazoles to the parent carbonyl compound:**

The procedure for preparation of the mixed ligand cobalt(II) complex has already been discussed in Chapter VII of the thesis.

1 mmol of the 2-arylbenzimidazole and 0.1 mmol of the mixed ligand Co(II) complex (0.0252g) was dissolved in methanol (10ml) and taken in a 100ml double necked round bottomed flask. The mixture was preheated to about 15 minutes at 60°C and the refluxed for a varying period of time as shown in the table IX.2. During the reflux 3ml of 30% H₂O₂ was added to the solution under reflux in three lots of equal volume over a period of 15 mins. The reaction was monitored with TLC on silica gel plates. After the end of the reaction as indicated by TLC, the reaction mixture was poured into a large volume of water. The aldehydes precipitated out and purified by preparative TLC. The aldehydes were confirmed by comparing GC-MS, IR and melting points with authentic samples.
## Table IX.2
Regeneration of aldehydes from 2-arylbenzimidazoles using Co(II) catalyst
(Ref. Scheme IX.17)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate(Ar)</th>
<th>Product Ar-CHO</th>
<th>Reflux time(min)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{NO}_2)</td>
<td>4-nitrobenzaldehyde</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>(\text{-CH}_3)</td>
<td>4-methylbenzaldehyde</td>
<td>25</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>(\text{N(CH}_3\text{)}_2)</td>
<td>N,N-dimethylaminobenzaldehyde</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>(\text{OCH}_3)</td>
<td>3,4-dimethoxybenzaldehyde</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>(\text{-Br})</td>
<td>4-bromobenzaldehyde</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>(\text{-OCH}_3)</td>
<td>4-methoxybenzaldehyde</td>
<td>25</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>(\text{-Cl})</td>
<td>4-chlorobenzaldehyde</td>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>(\text{-Cl})</td>
<td>2-chlorobenzaldehyde</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>(\text{-Cl})</td>
<td>3-chlorobenzaldehyde</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>(\text{benzaldehyde})</td>
<td>Benzaldehyde</td>
<td>35</td>
<td>65</td>
</tr>
</tbody>
</table>
Generation of the parent aldehyde from 2-arylbenzoxazoles:

In a similar manner, the 2-arylbenzoxazoles obtained from aromatic aldehydes according to a procedure mentioned in chapter IV have been converted back to the parent aromatic aldehyde using the tetraethylammonium bromate. The preparation of the tetraethylammonium bromate has already been mentioned in Chapter V and the procedure adopted for generation of the parent carbonyl compounds from 2-arylbenzoxazole is shown in the scheme IX. 18.

![Scheme IX. 18](image)

Procedure of conversion of 2-arylbenzoxazoles to the parent carbonyl compound:

1 equivalent of benzoxazole dissolved in a methanol(10ml) and taken in a 100ml double necked round bottomed flask. To this was added 1 equivalent of tetraethylammoniumbromate and refluxed for varying amount of time as shown in the table IX.3. At the end of the reaction as indicated by TLC, the reaction mixture was added to a large volume of water. The product aldehydes precipitated out and were identified by comparing their melting points and IR spectra with authentic samples. GC-MS analysis was also helpful in identifying the regenerated aldehyde.
### Table IX.3
Regeneration of aldehydes from 2-arylbenzoxazoles using tetraethylammonium bromate
(Ref. Scheme IX.18)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate(Ar)</th>
<th>Product Ar-CHO</th>
<th>Reflux time(min)</th>
<th>Yield(%)</th>
<th>M.Pt. (Lit.)</th>
<th>Molecular Ion(MH)+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO₂</td>
<td>4-nitrobenzaldehyde</td>
<td>75</td>
<td>72</td>
<td>106</td>
<td>151</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>4-methylbenzaldehyde</td>
<td>55</td>
<td>85</td>
<td>--</td>
<td>110</td>
</tr>
<tr>
<td>3</td>
<td>N(CH₃)₂</td>
<td>N,N-dimethylaminobenzaldehyde</td>
<td>70</td>
<td>75</td>
<td>74</td>
<td>149</td>
</tr>
<tr>
<td>4</td>
<td>OCH₃</td>
<td>3,4-dimethoxybenzaldehyde</td>
<td>60</td>
<td>75</td>
<td>42-45</td>
<td>166</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>4-bromobenzaldehyde</td>
<td>60</td>
<td>80</td>
<td>55-58</td>
<td>185</td>
</tr>
<tr>
<td>6</td>
<td>OCH₃</td>
<td>4-methoxybenzaldehyde</td>
<td>50</td>
<td>80</td>
<td>--</td>
<td>136</td>
</tr>
<tr>
<td>7</td>
<td>Cl</td>
<td>4-chlorobenzaldehyde</td>
<td>60</td>
<td>67</td>
<td>47</td>
<td>140.5</td>
</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>2-chlorobenzaldehyde</td>
<td>50</td>
<td>85</td>
<td>--</td>
<td>140.5</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>3-chlorobenzaldehyde</td>
<td>75</td>
<td>70</td>
<td>--</td>
<td>140.5</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Benzaldehyde</td>
<td>50</td>
<td>65</td>
<td>--</td>
<td>106</td>
</tr>
</tbody>
</table>

**Conclusion:**
From the experiments carried out and as elaborated herein, it is evident the regeneration of carbonyl compounds from 1,1-diacetates can be carried out in aqueous medium in the presence of a detergent. The conditions are not too vigorous. Further, 2-arylbenzimidazoles and 2-arylbenzoxazoles can also be transformed back to the parent carbonyl compound using oxidants such as H₂O₂ in the presence of mixed ligand Co(II) complex as the catalyst and the tetraethylammonium bromate respectively.
MASS SPECTRUM OF 4-methylbenzaldehyde
MASS SPECTRUM OF
"4-methoxybenzaldehyde"
MASS SPECTRUM OF
"3-chlorobenzaldehyde"
References:

2. Kocienski, P. in Protecting groups; Thieme: Stuttgart, 1994


