Chapter-4

Synthesis of 1,1-diacetics from aldehydes
4.1 Introduction

One of the important strategies in devising organic synthesis is the protection and deprotection of functional groups. Selective protection of carbonyl function as acylals is an important transformation in organic chemistry because of their stability under neutral and basic conditions as well as under critically controlled acidic conditions.\textsuperscript{1-3} Acylals have been also used as substrates for nucleophilic substitution reactions.\textsuperscript{4-5} As synthons, they have been exploited in well known reactions of organic chemistry, like Grignard,\textsuperscript{6} Barbier,\textsuperscript{7} Knoevenagel,\textsuperscript{8} and benzoin type reactions,\textsuperscript{9} and have been also used in total synthesis of sphingofungins E and F.\textsuperscript{10} Their utility in the cotton\textsuperscript{11} and other industries have been also well established.\textsuperscript{12} Acylals are also important building blocks for the synthesis of dienes for Diels-Alder cycloaddition reaction.\textsuperscript{13} The relative acid stability of acylal is another interesting feature in the field of protection and deprotection chemistry.

General, acylals are prepared by treating aldehydes with acetic anhydride under acidic conditions. Strong proton acids such as sulfuric acid, phosphoric acid, methanesulphonic acid,\textsuperscript{14} Nafion-H,\textsuperscript{15} heteropoly acids,\textsuperscript{16} and Lewis acids, such as zinc chloride, ferric chloride and phosphorus trichloride\textsuperscript{17} have been employed as catalysts. Some more catalysts are also discussed in literature survey.
4.2 Literature survey

J. S. Yadav et al.,\textsuperscript{18} reported that Aldehydes are chemoselectively converted into the corresponding \textit{gem}-diacetates at ambient temperature in high to quantitative yields using a catalytic amount of indium(III) chloride. The deprotection of the resulting \textit{gem}-diacetates is achieved using the same catalyst in the presence of water.

\textbf{S. C. Roy et al.,}\textsuperscript{19} developed an efficient method for the chemoselective synthesis of \textit{geminal} diacetates (acylals) from aldehydes using acetic anhydride in the presence of a catalytic amount of Ceric ammonium nitrate in excellent yield. Ketones are found to be unaffected under the reaction conditions. The deprotection of acylals by using water and Ceric ammonium nitrate has also been achieved.
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**synthesis of Acylals**

A.K. Mishra et al.,\(^{20}\) reported a mild and efficient method for the preparation of acylals from aldehydes in the presence of catalytic amounts of HClO\(_4\)-SiO\(_2\) under solvent-free conditions in very good to excellent yields.

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\end{array}
\xrightarrow{\text{Ac}_2\text{O} \ (1.5 \text{ eq}), \ \text{HClO}_4\text{-SiO}_2 \ (2.5 \text{ mol\%})} 
\begin{array}{c}
\text{O} \\
\text{OAc} \\
\end{array}
\]

neat, RT

B. Karimi et al.,\(^ {21}\) described that a variety of alcohols and aldehydes were reacted with acetic anhydride at room temperature in the presence of a catalytic amount of lithium triflate (LiOTf) to produce the corresponding esters and 1,1-diacetates, respectively, in good to excellent yields under essentially neutral reaction conditions.

\[
\begin{array}{c}
\text{OH} \\
\end{array}
\xrightarrow{\text{Ac}_2\text{O} \ (6 \text{ eq}), \ \text{LiOTf} \ (0.3 \text{ eq})} 
\begin{array}{c}
\text{OAc} \\
\end{array}
\]

neat, RT, 30h

\[
\begin{array}{c}
\text{TBDMSO} \\
\text{CHO} \\
\end{array}
\xrightarrow{\text{Ac}_2\text{O} \ (8 \text{ eq}), \ \text{LiOTf} \ (0.2 \text{ eq})} 
\begin{array}{c}
\text{TBDMSO} \\
\text{OAc} \\
\end{array}
\]

neat, RT, 26h
T. S. Jin et al.,\textsuperscript{22} reported a facile and efficient method for synthesis of 1,1-diacetates from aldehydes with acetic anhydride has been carried out in excellent yield in the presence of H$_2$NSO$_3$H.

\[ \text{R-CHO} + \text{Ac}_2\text{O} \xrightarrow{\text{H}_2\text{NSO}_3\text{H}} \text{R-CH(OAc)$_2$} \]

N. Sumida et al.,\textsuperscript{23} reported that variety of aldehydes react with acid anhydrides in the presence of a catalytic amount of lithium tetrafluoroborate to afford the corresponding geminal dicarboxylates (acylals) in good to excellent yields.

B. Karimi et al.,\textsuperscript{24} described that Aldehydes react with acetic anhydride in the presence of a catalytic amount of N-bromosuccinimide (NBS) to give their corresponding 1,1-diacetates (gem-diacetates) in good to excellent yields.

\[ \text{RCHO} \xrightarrow{\text{Ac}_2\text{O}, \text{NBS}} \text{AcO} \text{R} \text{OAc} \]

J. C. Sarma et al.,\textsuperscript{25} described an efficient method for synthesis of 1,1-diacetates from aldehydes with acetic anhydride in the presence of catalytic amount of iodine under CHCl$_3$ solvent.
J. C. Sarma et al.,\textsuperscript{26} reported that a variety of aldehydes react with acetic anhydride in the presence of trimethylchlorosilane and sodium iodide or trimethylchlorosilane alone to afford 1,1-diacetates in excellent yields.

X. Zhang et al.,\textsuperscript{27} described that Fe$_2$(SO$_4$)$_3$·xH$_2$O as an efficient heterogeneous catalyst for the preparation of gem-dicarboxylates (acylals) from aldehydes at ambient temperature, under solvent-free conditions.

A. K. Chakraborti et al.,\textsuperscript{28} reported that 1,1-diacetates are formed in excellent yields from aldehydes and acetic anhydride under solvent-free conditions at room temperature in short times in the presence of a catalytic amount of copper(II) tetrafluoroborate hydrate.

S. A. Pourmousavi et al.,\textsuperscript{29} described a method for a variety of aldehydes which react with acetic anhydride in the presence of a catalytic amount of H$_2$SO$_4$-Silica to afford the corresponding 1,1-diacetates (acylals) in excellent yields. Ketones are not affected under the reaction conditions.
These are the reported methods for the synthesis of 1,1-diacetates from aldehydes. Although some of these methods have convenient protocols with good to high yields, the majority of these methods suffer at least from one of the following disadvantages: reaction under oxidizing conditions, prolonged reaction time, high temperatures, use of moisture-sensitive and expensive catalysts, use of solvents, strong conditions, difficulty in scaling up, etc. Therefore, development of catalysts working under mild reaction conditions is desirable.

In recent years, heterogeneous catalysts have gained importance in several organic transformations due to their interesting reactivity as well as for economic and environmental reasons. We observed that silica supported sodium hydrogen sulphate is a highly efficient catalyst for the synthesis of 1,1-diacetates (acylals) from the reaction of aldehydes with acetic anhydride under solvent-free conditions. The catalyst NaHSO₄-SiO₂ can easily be prepared from the readily available NaHSO₄ and silica gel (230–400 mesh) and these are inexpensive and nontoxic as the reaction is heterogeneous in nature, so the catalyst can easily removed by simple filtration.
Main objective of the present work

This chapter deals with the synthesis of 1,1-diacetates (acylals) from the reaction of aldehydes with acetic anhydride in the presence of silica supported sodium hydrogen sulphate as a catalyst. The chemoselectivity of the catalyst also investigated.

4.3 Results and Discussion

Here a extremely convenient, mild, and highly chemoselective procedure for the conversion of aldehydes to the corresponding acylals in the presence of acetic anhydride and catalytic amount of NaHSO₄-SiO₂ under solvent-free conditions was reported. Initially an attempt was made for the acylation reaction of benzaldehyde with acetic anhydride in the presence of NaHSO₄-SiO₂. The treatment of 1 equivalent of benzaldehyde with 4 equivalents of acetic anhydride in the presence of NaHSO₄-SiO₂ (25%/wt) afforded corresponding acylal in a short time in almost quantitative yield. In a controlled experiment, it was observed that the reaction does not take place in the absence of silica supported sodium hydrogen sulphate. To optimize the reaction conditions, it was tried to convert benzaldehyde to its corresponding acylal in various solvents and also under solvent-free conditions (Table-1)
Table-1  conversion of benzaldehyde to its corresponding diacetate in different solvents and under solvent-free conditions in the presence of NaHSO$_4$-SiO$_2$ at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time(min)</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl acetate</td>
<td>25</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>Acetonitrile</td>
<td>30</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>35</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>Dichloromethane</td>
<td>40</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>Solvent-free</td>
<td>15</td>
<td>94</td>
</tr>
</tbody>
</table>

$^a$isolated yields.

As shown in Table-1, in comparison to conventional methods in solution the yield of the reaction under solvent-free conditions is higher and the reaction time is shorter. Therefore, the above conditions were employed for the conversion of various aldehydes to the corresponding acylals under solvent-free conditions (Table-2).
Scheme-1

Table-2. Formation of acylals using NaHSO₄-SiO₂ under solvent-free conditions at room temperature.ᵃ

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time(min)</th>
<th>Yield(%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="substrate_image" alt="image" /></td>
<td>![product_image]</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td><img src="substrate_image" alt="image" /></td>
<td>![product_image]</td>
<td>20</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td><img src="substrate_image" alt="image" /></td>
<td>![product_image]</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td><img src="substrate_image" alt="image" /></td>
<td>![product_image]</td>
<td>15</td>
<td>91</td>
</tr>
</tbody>
</table>

ᵃ: Some details or conditions may be missing from the image. The table shows the formation of acylals using NaHSO₄-SiO₂ under solvent-free conditions at room temperature.

ᵇ: The yield values might require additional context to fully understand.


<table>
<thead>
<tr>
<th></th>
<th><img src="image1.png" alt="Chemical Structure" /></th>
<th><img src="image2.png" alt="Chemical Structure" /></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
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<td>89</td>
</tr>
<tr>
<td>6</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
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<td>84</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Chemical Structure" /></td>
<td><img src="image8.png" alt="Chemical Structure" /></td>
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<td>90</td>
</tr>
<tr>
<td>8</td>
<td><img src="image9.png" alt="Chemical Structure" /></td>
<td><img src="image10.png" alt="Chemical Structure" /></td>
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<td>85</td>
</tr>
<tr>
<td>10</td>
<td><img src="image13.png" alt="Chemical Structure" /></td>
<td><img src="image14.png" alt="Chemical Structure" /></td>
<td>15</td>
<td>87</td>
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</tbody>
</table>

*Reaction conditions: benzaldehyde (1 mmol), Ac₂O (4 mmol) and NaHSO₄-SiO₂ (25%/wt) were stirred at RT under solvent-free conditions, isolated yields.*

The results listed in Table-2 show that both aromatic and aliphatic aldehydes react smoothly with acetic anhydride to afford the corresponding geminal diacetates in good to excellent yields. Aromatic aldehydes possessing electron-withdrawing substituents, halogens and electron-releasing substituents on the aromatic ring
afforded the corresponding acylals in excellent yields and in short reaction times. Nitro substituted aldehydes also gave good yields, but aldehydes having powerful electron-releasing substituent like OMe are slightly decreased the yield and increased the reaction time.

In order to show the high selectivity of the method, competitive reactions method was studied for the acylation of aldehydes in the presence of ketones using silica supported sodium hydrogen sulphate as a catalyst. When acetophenone was used in this reaction, no corresponding product was isolated by using this catalytic system, this result indicates that the chemoselective protection of an aldehyde in the presence of ketone could be achieved by this procedure. (Scheme 2)

One interesting property of the silica supported sodium hydrogen sulphate catalyst is its heterogeneous catalytic process. Thus, recovery of the catalyst is very convenient. After the reactions, the catalyst was recovered by filtration. The activity of the recovered catalyst was carefully investigated through the reaction of benzaldehyde and acetic anhydride under solvent-free conditions. Good yields
were obtained and the sample composition remained unchanged even after the catalyst had been recycled for a third time.

Table-3. The synthesis of acylal from benzaldehyde and acetic anhydride in the presence of recycled NaHSO₄-SiO₂.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycle</th>
<th>Time(min)</th>
<th>Yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; use</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; use</td>
<td>20</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; use</td>
<td>30</td>
<td>77</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield.

4.4 Conclusion

In conclusion, NaHSO₄-SiO₂ is a chemoselective and highly efficient catalyst for acylal formation from aldehydes. The advantages of this methodology over the reported methods is the availability of the starting materials, simplicity of acylation procedure, a clean work-up, a short reaction time, and high yields. The catalyst system is a free flowing powder that can be stored at room temperature for several months without losing its catalytic potentiality and it may be considered a very cheap source of solid supported acidic catalyst compared to other commercially available expensive solid supported acids. However, preparation of NaHSO₄-SiO₂ is straight forward and handling of the reagent is also easy. In addition, this reagent acts as an insoluble catalyst that could be removed from the
reaction mixture by simple filtration and compliance with the green chemistry protocols.

4.5 Experimental Section

All the melting points were determined from the open capillary method and were uncorrected. The $^1$H and $^{13}$C NMR were recorded on 400 MHz Varian FT-NMR spectrometer with tetramethylsilane (TMS) as the internal standard. The solvents used for NMR analysis were CDCl$_3$. The infrared (IR) spectra were obtained using Perkin-Elmer’s FT-IR spectrophotometer. The mass spectra were recorded on Waters ZQ-4000 equipped with ESI and API mass detector. The Carbon, Hydrogen and Nitrogen (CHN) analysis was done on Perkin-Elmer PE 2400 Series II machine.

The thin layer chromatography (TLC) was performed either using the Merck precoated TLC plates or on ACME’s silica gel with 13% calcium sulphate (CaSO$_4$) as binder and the components were visualized under iodine chamber or by UV exposure or by the potassium permanganate (KMNO$_4$) spray technique. Flash column chromatography was performed using Merck silica gel (100-200 mesh). The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Spectrochem, and Sisco research laboratories (SRL), and they were used without purification prior to use.
General experimental procedure for the preparation of acylals:

A mixture of aldehyde (1 mmol), freshly distilled Ac$_2$O (4 mmol) and NaHSO$_4$-SiO$_2$ (25%/wt) was stirred at room temperature and the progress of the reaction was monitored by TLC Hexane: EtOAc (9:1). After completion of the reaction, the reaction mixture was diluted with EtOAc and the catalyst was removed by filtration. Obtained filtrate was washed with saturated NaHCO$_3$ solution and water and dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure to get the crude product and was purified by column chromatography to give pure acylal compound.
4.6 Physical, Spectral and Analytical Data of compounds (Table-2 and Table-4)

Phenylmethylene diacetate (Table-2, Entry-1)

Yield: 94%, off-white solid; m.p: 45-46°C; $^1$H NMR (CDCl$_3$): δ 7.63 (s, 1 H), 7.53-7.50 (m, 2 H), 7.40-7.36 (m, 3 H), 2.11 (s, 6 H); IR (KBr, cm$^{-1}$): 3068, 1756, 1504, 1440, 1010; Anal. Calcd. For C$_{11}$H$_{12}$O$_4$: C, 63.45; H, 5.81; O, 30.74. Found: C, 63.71; H, 5.70.

(4-Chlorophenyl) methylene diacetate (Table-2, Entry-2)

Yield: 88%, Colourless solid; m.p: 82-84°C; $^1$H NMR (CDCl$_3$): δ 7.63 (s, 1 H), 7.46 (d, J=8.4 Hz, 2 H), 7.38 (d, J=8.4 Hz, 2 H), 2.12 (s, 6 H); $^{13}$C NMR (CDCl$_3$) δ: 20.76, 20.87, 89.0, 89.13, 128.14, 128.85, 133.97, 135.72, 168.67; IR (KBr, cm$^{-1}$): 3465, 3019, 2924, 1769, 1745, 1492, 1373, 1241, 1070, 1006; Anal. Calcd. For C$_{11}$H$_{11}$ClO$_4$: C, 54.45; H, 4.57; Cl, 14.61; O, 26.37. Found: C, 54.36; H, 4.68.
(4-Bromophenyl) methylene diacetate (Table-2, Entry-3)

![Chemical Structure of (4-Bromophenyl) methylene diacetate]

Yield: 90%, off-white solid; m.p: 83-85 °C; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.64 (s, 1H), 7.57-7.54 (m, 2H), 7.42-7.40 (m, 2H), 2.12 (s, 6H).

\(P\)-Tolyl methylene diacetate (Table-2, Entry-4)

![Chemical Structure of \(P\)-Tolyl methylene diacetate]

Yield: 91%, white solid; m.p: 81-83 °C; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.64 (s, 1H), 7.41 (d, \(J=8\) Hz, 2H), 7.21 (d, \(J=8\) Hz, 2H), 2.37 (s, 3H), 2.12 (s, 6H).

(2-Methoxyphenyl) methylene diacetate (Table-2, Entry-5)

![Chemical Structure of (2-Methoxyphenyl) methylene diacetate]

Yield: 89%, Colourless solid; m.p: 69-71 °C; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.02 (s, 1H), 7.48 (m, 1H), 7.38 (m, 1H), 7.01 (m, 1H), 6.90 (d, \(J=8.2\) Hz, 1H), 3.84 (s, 3H), 2.11 (s, 6H).
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(4-Methoxyphenyl) methylene diacetate (Table-2, Entry-6)

Yield: 84%, Colourless solid; m.p: 64-65 °C; \(^1\)H NMR (CDCl\(_3\)): δ 7.62 (s, 1 H), 7.45 (d, \(J\)=8.8 Hz, 2 H), 6.92 (d, \(J\)=8.8 Hz, 2 H), 3.82 (s, 3 H), 2.11 (s, 6 H); \(^{13}\)C NMR (CDCl\(_3\)) δ: 20.81, 20.92, 55.48, 89.68, 89.81, 113.89, 114.30, 128.15, 131.92, 160.59, 168.80; IR (KBr, cm\(^{-1}\)): 3462, 3014, 2937, 1749, 1618, 1378, 1244, 1207, 1018, 936; Anal. Calcd. For C\(_{12}\)H\(_{14}\)O\(_5\); C, 60.50; H, 5.92; O, 33.58. Found: C, 60.98; H, 5.66.

(2-Nitrophenyl) methylene diacetate (Table-2, Entry-7)

Yield: 90%, off-white solid; m.p: 86-88 °C; \(^1\)H NMR (CDCl\(_3\)): δ 8.21 (s, 1H), 8.05 (d, \(J\)=9 Hz, 1H), 7.73 (m, 1H), 7.62 (m, 2H), 2.12 (s, 6H).

(4-Nitrophenyl) methylene diacetate (Table-2, Entry-8)
Yield: 94%, light pale yellow solid; m.p: 124-126 °C; $^1$H NMR (CDCl$_3$): $\delta$ 8.2 (d, $J$= 8.8 Hz, 2H), 7.74 (s, 1H), 7.71 (d, $J$= 8.8 Hz, 2H), 2.12 (s, 6H).

**Furan-2-yl methylene diacetate (Table-2, Entry-9)**

Yield: 85%, Colourless solid; m.p: 50-52 °C; $^1$H NMR (CDCl$_3$): $\delta$ 7.76 (s, 1H), 7.38 (m, 1H), 6.59 (m, 1H), 6.42 (m, 1H), 2.11 (s, 6H).

**Butane-1,1-diyldiacetate (Table-2, Entry-10)**

Yield: 87%, Colourless oil; $^1$H NMR (CDCl$_3$): $\delta$ 6.80 (t, $J$= 5.5 Hz, 1H), 2.11 (s, 6H), 1.79-1.77 (m, 2H), 1.45-1.42 (m, 2H), 0.94 (t, $J$= 3.5 Hz, 3H).
Figure 1: $^1$H NMR Spectrum of (4-chlorophenyl) methylene diacetate
Figure 2: $^{13}$C NMR Spectrum of (4-chlorophenyl) methylene diacetate
Figure 3: IR Spectrum of (4-chlorophenyl) methylene diacetate
Figure 4: $^1$H NMR Spectrum of (4-methoxyphenyl) methylene diacetate.
Figure 5: $^{13}$C NMR Spectrum of (4-methoxyphenyl) methylene diacetate
Figure 6: IR Spectrum of (4-methoxyphenyl) methylene diacetate