CHAPTER V

Use of Diacetoxyiodobenzene in Organic Synthesis.

Section A : Synthesis of 2,3-Dihydrofuran Derivatives
Section B : Synthesis of Oxazole Derivatives
CHAPTER V

Section A: Synthesis of 2,3-Dihydrofuran Derivatives

The points to be studied:

1. Importance of Dihydrofuran Derivatives

2. Literature Survey for the Synthesis of Dihydrofuran Derivatives

3. Present Work

4. Results and Discussions

5. Proposed Reaction Mechanism

6. Experimental Section

7. Spectral Analysis

8. Merits of the Methodology and Conclusion

9. References
1] Importance of Dihydrofuran Derivatives

Dihydrofuran and furans are two of the most important heterocycles with widespread occurrence in nature. They are important constituent in biologically active natural products such as terpenoids arising from plants and animals. The common examples of naturally occurring furanoterpenoids are evodone (1), menthofuran (2) and maturone (3).

The natural products containing a furan ring have an intense odour, e.g. 2-furymethanethiol (4), a component of coffee aroma and rose furan (5), a component of rose oil.

Possessing a variety of biological activities, they are used as pharmaceutical, flavor, insecticidal and fish antifeedant. Their important biological activities and usefulness as synthetic intermediates of natural products have prompted a search for better method of synthesis of fused ring dihydrofurans and furans.
2] Literature Survey for the Synthesis of Dihydrofuran Derivatives

Majority of literature methods for the synthesis of dihydrofuran derivatives originate from the oxidative addition of 1,3-dicarbonyl compounds to olefins in presence of a suitable catalyst. The following few important methods for the synthesis of fused ring dihydrofurans and dihydrofurans is explained below.

2.1] Base Catalyzed Condensation between Allenic Sulfonium Salt and β-Dicarbonyl Compounds

The allenic sulfonium salt (6) is a reactive electrophile. It reacts with enolate anions of an acyclic and cyclic 1,3-dicarbonyl compounds to afford substituted furans (8). The intermediate (8) is somewhat unstable and get easily isomerized by treatment with p-TsOH to get 3-methylfurans in good to excellent yields.

- Using this methodology, a practical synthesis of naturally occurring furanoterpenoids such as evodone (1), menthofuran (2) and maturone (3) has been achieved.
The method requires a separate preparation of allenic sulfonium salt which is obtained by the reaction of propargyl bromide and dimethyl sulfide.  

Basic medium of the reaction can induce aldol related side reactions.

2.2] Single Electron Oxidant Mediated Oxidative Addition of \( \beta \) - Dicarbonyl Compounds to Olefins

The single electron oxidant like ceric (IV) ammonium nitrate and manganese (III) acetate has been used in the synthesis of dihydrofuran derivative through oxidative addition of 1,3-dicarbonyl compounds to olefins.

\[
\begin{align*}
\text{R}^1 \quad \text{R}^2 \\
\text{R}^1 \quad \text{R}^2
\end{align*}
\]

The reaction of dimedone, acetylacetone and ethyl acetoacetate with cyclic and acyclic alkenes in presence of CAN gives dihydrofurans in good yields.

Simple and mild reaction conditions is an important advantage of this procedure.

Styrenic olefins are susceptible for free radical polymerization in presence of single electron oxidant. So an excess of olefins is needed.

The yields of the reactions are relatively poor for CAN as well as Mn(OAc)\(_3\) mediated procedure ranging from 20 to 60%.

Reaction is sometimes accompanied by side reactions.
2.3] Rhodium (II) Catalyzed Reaction of Cyclic Diazodicarbonyl Compounds with Allyl Halides

The rhodium catalyzed decomposition of cyclic diazodicarbonyl compounds in presence of allyl halide is an important method for the synthesis of fused dihydrofuran derivatives. For example:

- The methodology is restricted only to cyclic 1,3-dicarbonyl compounds.
- The yields of reaction are very quantitative with only allyl iodides whereas with allyl chlorides and bromides, the yields of dihydrofuran derivatives are measurably low.
- The reaction is expected to proceed through halonium ylides. The chloronium and bromonium ylides are more stable than iodonium ylides. So the reaction with allyl chloride and bromides is always
accompanied by side products originating from \([2,3]\) sigmatropic rearrangement\(^9\).

\[
\begin{array}{c}
\text{Rh}_2(OAc)_4 \quad \text{hv (400w)} \quad \text{CH}_3\text{CN} \\
\begin{array}{c}
\text{N}_2 \\
\text{O} \\
\text{O} \\
\text{R}_2 \quad \text{Cl} \quad \text{Cl} \\
\text{Br} \quad \text{O} \quad \text{O} \\
\text{O} \quad \text{O} \quad \text{Br} \\
\end{array}
\end{array}
\]

\[\begin{array}{c}
\text{75\%} \\
\text{60\%} \\
\text{12\%} \\
\text{15\%}
\end{array}\]

\([2,3]\) sigmatropic rearrangement products

2.4] Photochemical Cycloaddition Reactions of Iodonium Ylides of Cyclic \(\beta\)-diketones with Olefins\(^{10}\)

The photochemical irradiation of a cyclic \(\beta\)-dicarbonyl iodonium ylide with olefins in acetonitrile gives substituted dihydrofurans in moderate to high yields.

\[
\begin{array}{c}
\text{R}_1 \quad \text{R}_2 \\
\text{O} \\
\text{O} \\
\text{R}_3
\end{array}
\begin{array}{c}
\text{R}_1 \quad \text{R}_2 \\
\text{O} \\
\text{O} \\
\text{R}_3
\end{array}
\]

- A separate preparation and isolation of iodonium ylides of cyclic \(\beta\)-diketones is required.
- The iodonium ylide (9) is only stable at very low temperature \(-30^\circ\text{C}\) for a few months.
- The thermal reaction of iodonium ylide (9) with olefins, in the presence of catalytic amounts of Cu(acac)$_2$ gives a complex mixture of inseparable products.$^{10b}$

- The reaction is suitable only for cyclic iodonium ylides.

2.5) Oxidative Addition of 1,3-dicarbonyl Compounds to Alkenes Under Aerobic Conditions Using Cobalt (II) Acetate$^{11}$

The reaction of 1,3-dicarbonyl compounds with various aliphatic olefins in presence of cobalt (II) acetate under aerobic conditions give dihydrofuran derivatives.

\[
\text{O} + \text{Co(OAc)$_2$} \xrightarrow{\text{O}_2} \text{CO$_2$Me} + \text{CO$_2$Me} + \text{CO$_2$OMe}
\]

- Aerobic experimental conditions are necessary for dihydrofuran formation.

- Anerobic conditions yield only alkylated product (12).

- Long reaction time of 8-15 hours.

The above discussed literature methods for the dihydrofuran formation are mainly focussed on the oxidative addition of 1,3-dicarbonyl compounds or their derivatives to a variety of olefins in presence of a suitable catalyst like NaOEt, CAN, Mn(OAc)$_3$, Rh$_2$(OAc)$_4$ and Co(OAc)$_2$. In other words, these methods are providing dihydrofuron skeleton through two important bond forming reactions namely C-C and C-O according to following analysis.
However, there are several reports in the literature for dihydrofurans formation, apart from the oxidative addition of β-dicarbonyl compounds to olefins. One of the such recent method is briefly highlighted in the following literature account.

2.6] From α-Alkenyl β-Ketoamides Using Iodine

α-Alkenyl β-Ketoamides undergo iodocyclization in presence of I₂/Na₂CO₃ to form iodinated 2,3-dihydrofurans.¹²

![Chemical reaction diagram]

It is a notable methodology promoting the formation of iodinated 2,3-dihydrofurans despite the possibility of formation of lactones and lactams by the iodocyclization of α-alkenyl-β-ketoamides.
3] Present Work

Herein we wish to report that a variety of olefins react with β-dicarbonyl compounds at 0 °C in the presence of diacetoxyiodobenzene to afford highly substituted 2,3-dihydrofuran derivatives in good to excellent yields.

We initiated the study by investigating the reaction of dimedone 1a with styrene 1b in the presence of DIB. When the above reaction mixture in acetonitrile was stirred at 0 °C for 1.5 hours, the 2,3-dihydrofuran derivative 1e was indeed formed in 71% yield (Scheme 1). The reaction conditions such as temperature and time were then examined in detail. When the above reaction was carried out at room temperature from 3 to 5 hours, the desired product was formed in only 21% yield. The use of acetonitrile as a solvent for this reaction was arbitrarily chosen. However, there was no formation of any product from the participation of acetonitrile as a solvent.

![Scheme 1](image)
4) Results and Discussions

In order to assess the generality of the methodology, DIB mediated oxidative addition was carried out with some representative alkenes and cyclic as well as acyclic 1,3-dicarbonyl compounds. The results are summarized in Table 1.

The reactions were carried out using one equivalent of diacetoxyiodobenzene in acetonitrile at 0 °C. In all the reactions iodobenzene was formed as a side product.

Reaction with Styrene Derived Olefins:

Aromatic olefins such as styrene (entry 1), cinnamyl acetate (entries 2, 8 and 11) and indene (entry 3) underwent oxidative addition to form the corresponding dihydrofuran derivatives. All the reactions are expected to proceed through the intermediacy of a stable benzyl carbocation. So the yields of the reactions are very good.

Reactions with Aliphatic Olefins:

Simple alkenes such as allyl chloride (entry 4) and 1-methylcyclohexene (entries 5 and 9) were rather unreactive and gave the corresponding products in inferior yields. This is attributed to the relative less stability of alkyl carbocation than benzyl carbocation.

Reaction with Electron Deficient Olefins:

The reaction between electron deficient olefins such as ethyl acrylate (entry 6), ethyl cinnamate (entry 7) and dinedone was also studied. Since the success of dihydrofuran formation revolves around trapping of the relatively 'stable carbocation' intermediate, no product formation occurred in the case of ethyl acrylate. However, ethyl cinnamate underwent regioselective addition to dinedone to form the dihydrofuran in 52 % yield.
Table 1: Oxidative addition of \( \beta \)-dicarbonyl compounds to olefins using Iodobenzenediacetate in CH\(_3\)CN at 0 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \beta )-Dicarbonyl compound</th>
<th>Olefin B</th>
<th>Product c</th>
<th>Time (h)</th>
<th>Yield a (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="image1" alt="Molecule A" /></td>
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<td><img src="image3" alt="Product" /></td>
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<td>71</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Molecule A" /></td>
<td><img src="image5" alt="Molecule B" /></td>
<td><img src="image6" alt="Product" /></td>
<td>1</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Molecule A" /></td>
<td><img src="image8" alt="Molecule B" /></td>
<td><img src="image9" alt="Product" /></td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Molecule A" /></td>
<td><img src="image11" alt="Molecule B" /></td>
<td><img src="image12" alt="Product" /></td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td><img src="image13" alt="Molecule A" /></td>
<td><img src="image14" alt="Molecule B" /></td>
<td><img src="image15" alt="Product" /></td>
<td>2</td>
<td>62</td>
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<td><img src="image16" alt="Molecule A" /></td>
<td><img src="image17" alt="Molecule B" /></td>
<td><img src="image18" alt="Product" /></td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td><img src="image19" alt="Molecule A" /></td>
<td><img src="image20" alt="Molecule B" /></td>
<td><img src="image21" alt="Product" /></td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td><img src="image22" alt="Molecule A" /></td>
<td><img src="image23" alt="Molecule B" /></td>
<td><img src="image24" alt="Product" /></td>
<td>2</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td><img src="image25" alt="Molecule A" /></td>
<td><img src="image26" alt="Molecule B" /></td>
<td><img src="image27" alt="Product" /></td>
<td>2</td>
<td>46</td>
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<tr>
<td>10</td>
<td><img src="image28" alt="Molecule A" /></td>
<td><img src="image29" alt="Molecule B" /></td>
<td><img src="image30" alt="Product" /></td>
<td>1.5</td>
<td>43</td>
</tr>
<tr>
<td>11</td>
<td><img src="image31" alt="Molecule A" /></td>
<td><img src="image32" alt="Molecule B" /></td>
<td><img src="image33" alt="Product" /></td>
<td>1</td>
<td>51</td>
</tr>
</tbody>
</table>

a) Yields refer to isolated products.
5] Reaction Mechanism

Mechanistically, the formation of dihydrofuran derivatives may proceed through the initial reaction of the fairly electrophilic DIB with the nucleophilic enol form of the 1,3-dicarbonyl compound to give the intermediate 1. There are two possible paths for the formation of dihydrofuran from this intermediate 1.

Path A: The tendency of intermediate 1 to expel iodobenzene converts the initial electron rich active methylene carbon in an electron deficient center through umpolung. Taking the advantage of this reactivity, olefin can be trapped by reactive methylene carbon via SN2 displacement process, to form a relatively stable carbocation 2 which is attacked by oxygen lone pair to form cyclic intermediate 3.

Path B: Alternatively, the olefinic ligand can approach again to electrophilic iodine with acetate anion dissociation to form a new intermediate 4. Then C-O bond formation will occur in intermediate 4 by trapping of a stable carbocation by carbonyl oxygen lone pair to form a cyclic iodo-intermediate 5. Again, the reductive elimination property of iodobenzene from 5 will promote C-C bond formation resulting in intermediate 3.

Finally, the acetate anion abstracts an acidic hydrogen from 3 to give the 2,3-dihydrofuran derivative 6 (Scheme 2).

This mechanism is assumed on the basis of well established literature evidences for the processes like ligand dissociation/association, ability of umpolung induction and the reductive elimination of iodobenzene. Conclusively, the following parameters for diacetoxyiodobenzene interprets the success of dihydrofuran formation.

1) Electrophilic nature of diacetoxyiodobenzene.
2) Reversal of polarity of reactive methylene carbon due to superleaving ability of iodobenzene.
3) Formation of a stable carbocation favoring SN2 attack.
4) Tendency of electrophilic iodine to assemble the reacting ligands around its coordination sphere.
Scheme 2

Abstraction of Acidic Hydrogen

Ligand Association/Dissociation

Path A
Reductive Elimination

Path B
Assembling Reacting Ligands

Cyclisation

Reductive Elimination
6] Experimental Section

All the chemicals used to carry out experimental work were of standard quality. The purity of chemicals were checked by routine tests like melting point, boiling point, thin layer chromatography, etc.

Diacetoxyiodobenzene was purchased from Lancaster and used as it was provided.

To a magnetically stirred solution of 1,3-dicarbonyl compound (3 mmol) and olefin (3 mmol) in acetonitrile (15 ml) was introduced diacetoxyiodobenzene (3 mmol). The reaction mixture was stirred at 0 °C for the time as mentioned in table 1. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was washed with water (10 ml), extracted with CH₂Cl₂ and dried over anhydrous sodium sulphate. Removal of the solvent and subsequent silica gel chromatography afforded the pure product. The column chromatography was performed using pet ether and ethylacetate in 7:3 proportion. The pet ether used is of 40-60 °C boiling range.

The iodobenzene formed as a side product was isolated during column chromatography and subsequently used for some other different purposes.
7] Characterization:

IR spectra were recorded on a Perkin-Elmer 137-E spectrometer. The $^1$H NMR spectra were recorded on a Bruker 300 MHz instrument and the chemical shifts were reported with TMS as an internal standard. The spectral analysis for few selected products is given below:

7.1] 2-Phenyl-6, 6-dimethyl-4,5,6,7-tetrahydrobenzofuran-4-one

- Obtained as Viscous Oil
- $^1$H NMR data:

<table>
<thead>
<tr>
<th>Chemical shift in δ ppm</th>
<th>No. of protons</th>
<th>Splitting</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>6H</td>
<td>s</td>
<td>two methyl groups</td>
</tr>
<tr>
<td>2.0</td>
<td>2H</td>
<td>s</td>
<td>CH$_2$ adjacent to double bond in cyclohexenone moiety</td>
</tr>
<tr>
<td>2.1</td>
<td>2H</td>
<td>s</td>
<td>CH$_2$ adjacent to &gt;C=O</td>
</tr>
<tr>
<td>3.6</td>
<td>2H</td>
<td>d</td>
<td>CH$_2$ present in dihydrofuran moiety</td>
</tr>
<tr>
<td>5.2</td>
<td>1H</td>
<td>t</td>
<td>CH flanked by oxygen and phenyl</td>
</tr>
<tr>
<td>7.1 to 7.7</td>
<td>1H</td>
<td>m</td>
<td>Aromatic protons</td>
</tr>
</tbody>
</table>

- IR(cm$^{-1}$) data:
  3012, 2957, 2843, 1712, 1604, 1468, 1254, 1095, 793.

- Elemental Analysis:

  Theoretical : C, 79.33; H, 7.43
  Found : C, 79.36, H, 7.41
7.2] 2-Phenyl-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo-furan-4-one

- Viscous Oil:

- $^1$HNMR data

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<th>Chemical shift in δ ppm</th>
<th>No. of protons</th>
<th>Splitting</th>
<th>Assignments</th>
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</thead>
<tbody>
<tr>
<td>1.0</td>
<td>6H</td>
<td>s</td>
<td>two methyl groups</td>
</tr>
<tr>
<td>1.2</td>
<td>3H</td>
<td>t</td>
<td>CH$_3$ adjacent to CH$_2$ in side chain</td>
</tr>
<tr>
<td>2.1</td>
<td>2H</td>
<td>s</td>
<td>CH$_2$ adjacent to double bond.</td>
</tr>
<tr>
<td>2.2</td>
<td>2H</td>
<td>s</td>
<td>CH$_2$ adjacent to C=O</td>
</tr>
<tr>
<td>3.3</td>
<td>2H</td>
<td>m</td>
<td>CH$_2$ adjacent to CH$_3$ in side chain</td>
</tr>
<tr>
<td>4.2</td>
<td>1H</td>
<td>d</td>
<td>CH adjacent to ester group</td>
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<tr>
<td>5.1</td>
<td>1H</td>
<td>d</td>
<td>CH flank by oxygen and phenyl</td>
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<tr>
<td>7.2</td>
<td>5H</td>
<td>m</td>
<td>Aromatic protons</td>
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</table>

- IR (cm$^{-1}$): 3023, 2984, 2879, 1732, 1605, 1437, 1403, 1214, 1089, 790, 768.

- Elemental Analysis:

  Theoretical: C, 72.38; H, 7.30

  Found: C, 72.31; H, 7.27
7.3] 4-Acetyl-3-acetoxymethyl-5-methyl-2-phenyl-2,3-dihydrofuran

- Viscous Oil
- \(^1\)HNMR data:

<table>
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<th>Chemical shift in δ ppm</th>
<th>No. of protons</th>
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</tr>
<tr>
<td>1.7</td>
<td>3H</td>
<td>s</td>
<td>CH\textsubscript{3} attached to double bond</td>
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<tr>
<td>2.1</td>
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<td>s</td>
<td>CH\textsubscript{3}CO</td>
</tr>
<tr>
<td>2.5</td>
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<td>CH adjacent to CH and CH\textsubscript{2}O</td>
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<tr>
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<td>CH\textsubscript{2}O moiety</td>
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<td>1H</td>
<td>d</td>
<td>CH flank by oxygen and phenyl</td>
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<tr>
<td>7.4</td>
<td>5H</td>
<td>m</td>
<td>Aromatic protons</td>
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</table>

- IR (cm\(^{-1}\)) data: 3012, 2988, 2879, 1735, 1604, 1456, 1196, 1083, 760, 697.

- Elemental Analysis:

  Theoretical: C, 70.07; H, 6.56

  Found: C, 70.03; H, 6.54
<table>
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<th>INDEX</th>
<th>FREQUENCY (PPM)</th>
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<td>22</td>
<td>0.813</td>
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</table>
Merits of the Methodology and Conclusion:

In literature report, the syntheses of dihydrofuran from iodonium ylides of \( \beta \)-diketones and alkenes in the presence of \( \text{Cu(acac)}_2 \) yields complex mixtures of inseparable products under thermal conditions.\(^{10}\) The yields of dihydrofurans are very low in the case of the single electron oxidant [CAN and \( \text{Mn(OAc)}_3 \)] mediated oxidative addition of \( \beta \)-dicarbonyl compounds to styrene derived olefins.\(^{7}\) This is due to the susceptibility of styrenic olefins to polymerization and therefore, an excess of olefins is needed. Thus it appears that the present methodology is quite advantageous in comparison to single electron oxidants and iodonium ylides procedures.

Apart from these advantages, the present methodology has the following merits:

1. Simple reaction work-up.
2. Mild reaction conditions.
3. Good yields.
4. Starting materials are easily available.
5. Eco-friendly nature of the reagent, DIB. Iodobenzene is biodegradable.
7. Recyclability of the side product iodobenzene for the fresh preparation of diacetoxyiodobenzene is feasible.

Conclusion

In conclusion, we have developed an efficient DIB mediated oxidative addition of \( \beta \)-dicarbonyl compounds to olefins resulting in a one-pot syntheses of highly substituted dihydrofuran derivatives. We hope that the present methodology
will be a useful synthetic entry in the demonstrative use of DIB for carbon-carbon bond formation reactions.
9] References:


CHAPTER V

Section B: Synthesis of Oxazole Derivatives

![Chemical Reaction]

The points to be studied:

1. Importance of Oxazole Derivatives
2. Literature Survey for the Synthesis of Oxazole Derivatives
3. Present Work
4. Results and Discussions
5. Proposed Reaction Mechanism
6. Experimental Section
7. Spectral Analysis
8. Merits of the Methodology and Conclusion
9. References
1] Importance of Oxazole Derivatives:

1,3-Oxazoles of various substitution pattern has gained importance in synthetic organic chemistry because:

1.1] It is a sub-structural unit of many natural products such as alkaloids.

1.2] It is also present in some valuable drugs with a particular substitution pattern.

1.3] It is a starting material in many organic synthetic transformations.

1.1] Oxazole as a Sub-structural Part of Natural Products

Oxazoles are rarely found in natural products. Naturally occurring oxazoles range in structure from relatively simple 2,5-disubstituted derivatives such as the 5-(indol-3-yl) oxazole alkaloids, pimprinine 1a and pimprinethine 1b, to the more complex 2,4 disubstituted compounds such as phenoxxan 2, calyculin A3 and rhizoxin.4

\[
\begin{align*}
1a & \quad R = \text{Me} \\
1b & \quad R = \text{Et}
\end{align*}
\]

1.2] Oxazole as a Part of Active Drugs

Only a few pharmaceuticals derived from oxazoles are in use. The anti-inflammatory and analgesic action of 2-diethylamino-4,5-diphenyloxazole is known.5 The structures of few drugs containing oxazole moiety is show below.

\[
\begin{align*}
3 & \quad \text{Anti-inflammatory and Analgesic} \\
4 & \quad \text{Griseoviridin as antibiotics}
\end{align*}
\]
Oxazoles as Optical Brighteners

Aryl-substituted oxazoles are strongly fluorescent. In solution, they are therefore suitable as luminous substances for liquid scintillation counters and also as optical brighteners (brightening agents). For example: 4,4'-bisoxazol-2-ylstibenes (5) are added to washing agents.

\[
\begin{array}{c}
\text{Me} \\
\text{N} \\
\text{O} \\
\text{Me} \\
\text{O} \\
\text{CH} = \text{CH} \\
\text{Me}
\end{array}
\]

During the washing process, they are absorbed by the fibers, so that the cloths appear to be 'whiter than white' as a result of blue fluorescence.

1.3] Synthetic Utility of Oxazole

Oxazoles are used as auxiliaries for transformations in organic synthesis in various ways.

Oxazoles can react as 1,3-dienes and therefore, it has tremendous synthetic utility in the multi-manipulative Diels-Alder reaction. For example, the industrial synthesis of vitamin B₆ (pyridoxine) is based on the success of oxazole’s participation in Diels-Alder reaction.

\[
\begin{array}{c}
\text{Me} \\
\text{N} \\
\text{O} \\
\text{Et} \\
\text{EtOH}
\end{array}
\] + \[
\begin{array}{c}
\text{COOEt} \\
\text{COOEt}
\end{array}
\] \text{key step} \xrightarrow{\Delta} \begin{array}{c}
\text{Me} \\
\text{N} \\
\text{O} \\
\text{Et} \\
\text{COOEt}
\end{array} \begin{array}{c}
\text{COOEt} \\
\text{EtOH}
\end{array}
\xrightarrow{\text{H}^+} \begin{array}{c}
\text{HO} \\
\text{Me}
\end{array} \begin{array}{c}
\text{CH}_2\text{OH} \\
\text{CH}_2\text{OH}
\end{array}
\xrightarrow{\text{LiAlH}_4} \begin{array}{c}
\text{HO} \\
\text{Me}
\end{array} \begin{array}{c}
\text{COOEt} \\
\text{COOEt}
\end{array}
\]

Vitamin B₆
2.1] Robinson-Gabriel Reaction

This involves the cyclodehydration of 2-acylamino carbonyl compounds \(1 (R^3 \neq H)\) to afford the synthesis of 2,5-disubstituted or 2,4,5-trisubstituted oxazoles 2.

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{O} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\end{array}
\xrightarrow{\text{Dehydrating Agent}}
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\end{array}
\]

- Classically this reaction is carried out with relatively harsh and toxic dehydrating agents such as concentrated \(\text{H}_2\text{SO}_4\), polyphosphoric acid, \(\text{P}_2\text{O}_5\), \(\text{SOCl}_2\), \(\text{POCl}_3\) and anhydrous \(\text{HF}\).\(^9\) Such dehydrating agents are relatively of little use when it's a matter of oxazole synthesis containing multiple functional groups.

- The required \(\alpha\)-acylamino ketones, 1 are accessible by two routes:
  
  A] Heating acid anhydrides with \(\alpha\)-amino acids in the presence of pyridine.
  
  B] Oxidation of \(\beta\)-hydroxyamides by the Dess-Martin reagent.\(^{10}\)

So Robinson-Gabriel synthesis directly/indirectly is a two step process.

- The oxidation of \(\beta\)-hydroxy amides with the Dess-Martin reagent, followed by a mild cyclodehydration of the intermediate \(\beta\)-keto amides with triphenylphosphine/I\(_2\), is a versatile extension of the Robinson-Gabriel reaction.\(^{11}\)
The separation of triphenylphosphine oxide from the final product oxazole is a relatively laborious job.

This two step protocol allows the rapid synthesis of highly substituted and functionalized oxazoles directly from readily available amino acid derivatives in good (55-81%) overall yields.

- Robinson-Gabriel approach is difficult for the cyclodehydration of aldehydo amides. This is because of the sensitivity of 2-acylamino aldehydes (1, R² = H) to oxidative and dehydrating conditions.¹²

- Recently, this problem is partially overcome by the cyclodehydration of 2-acylamino carbonyl compounds with Burges reagent under monomode microwave irradiation.¹³

2.2] Use of Rhodium (II) Acetate in Oxazole Synthesis

Rhodium (II) acetate has been successfully used in oxazole synthesis by means of two different ways.
A] A one pot synthesis of 4-carbomethoxy-5-methoxy-1,4-oxazole was achieved by the reaction of diethyl diazomalonate with nitriles in presence of rhodium (II) acetate.\textsuperscript{14}

\[ \text{MeO} \backslash \text{C} \backslash \text{O} \text{Me} + \text{RCN} \xrightarrow{\text{Rh}_2(\text{OAc})_4, \text{CHCl}_3, \text{reflux}} \text{MeO}_2\text{C} \backslash \text{N} \text{O}_\text{Me} \]

The reaction is expected to proceed through carbene intermediate.

This reaction is successfully applied in the total synthesis of 5-(indol-3-yl) oxazole alkaloids 1.

\[ \text{H} \backslash \text{C} \backslash \text{N}_2 \xrightarrow{\text{R} \text{--C} \equiv \text{N}, \text{Rh}_2(\text{OAc})_4} \text{BoC} \]

However, this methodology is less satisfactory for complex nitriles containing additional functional groups.

B] In another report, Rhodium (II) acetate has been used to prepare 2-acylaminoketones by the N-H insertion reaction of diazocarbonyl compounds with amide. The 2-acylaminoketone, a starting material of Robinson-Gabriel reaction, is then cyclodehydrated by using PPh\textsubscript{3}/I\textsubscript{2} combination.\textsuperscript{15}
This methodology has an appreciable success compared to previous "one pot" strategy because it can tolerate many functional groups, particularly protected NH$_2$ as Cbz-NH and protected aldehyde as acetals.$^{16}$

Needless to mention, both the strategy (A and B) require a separate preparation of diazodicarbonyl compound as a key intermediate.

2.3 Use of Hypervalent Iodine Reagents in Oxazole Synthesis

Three different hypervalent iodine reagents have been used in the oxazole synthesis.

1. Diacetoxyiodobenzene (DIB)

A facile one-pot synthesis of oxazole is reported by the coupling reaction of aromatic α-methyl ketones and nitriles of presence of diacetoxyiodobenzene.$^{17}$
A similar oxazole synthesis is reported by using thallium (III) acetate.\textsuperscript{18}

\[
\begin{align*}
\text{Ar} & \quad \text{RCOCH}_2R' \quad \text{MeCN, A} \quad \xrightarrow{\text{HTI}} \quad \text{RCOCHR'} \quad \text{MeCN, \Delta} \\
\text{MeCN, rt, 10 min.} & \quad \text{1.5 - 2h reflux} \\
\end{align*}
\]

The success of both the methodologies revolves around the conversion of aromatic $\alpha$-methyl ketones to $\alpha$-ketotriflates. However, thallium reagent is inherently toxic whereas DIB is ecofriendly.

2. [Hydroxy (Tosyloxy) Iodo] Benzene (HTI)

Enolizable ketones and related keto compounds are $\alpha$-functionalized by HTI. Based upon this idea, two different novel methodologies have been reported for oxazole synthesis.

A[ One-Pot Synthesis of 2,4-disubstituted oxazole\textsuperscript{19}]

\[
\begin{align*}
\text{CH}_3 & \quad \text{R}_1 \quad \text{CH}_3CN \quad \xrightarrow{\text{HTI}} \quad \text{R}_1 \quad \text{NH}_4\text{Ac} \\
\text{R}_2\text{COOH, Et}_3\text{N} & \quad \text{R}_2\text{AcOH} \\
\end{align*}
\]

$R_1 = \text{Ph, 4-ClC}_6\text{H}_4, 4-\text{CH}_3\text{OC}_6\text{H}_4, 4\text{NO}_2\text{C}_6\text{H}_4$

$R_2 = \text{Ph, 4-NO}_2\text{C}_6\text{H}_4$
B) Microwave associated 2,4,5-trisubstituted oxazole\(^{20}\)

\[
\begin{align*}
\text{R}^1 \text{C} = \text{O} \text{R}^2 & \quad \xrightarrow{\text{HDNIB}} \quad \xrightarrow{\text{MWI}} \quad \text{MWI} \\
20-40 \text{sec.} & \quad \text{ODNS} \\
\text{MWI} & \quad 1-2 \text{ min.} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 \text{C} = \text{O} \text{R}^2 & \quad \xrightarrow{\text{HDNIB}} \quad \xrightarrow{\text{MWI}} \quad \text{MWI} \\
20-40 \text{sec.} & \quad \text{ODNS} \\
\text{MWI} & \quad 1-2 \text{ min.} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 \text{C} = \text{O} \text{R}^2 & \quad \xrightarrow{\text{HDNIB}} \quad \xrightarrow{\text{MWI}} \quad \text{MWI} \\
20-40 \text{sec.} & \quad \text{ODNS} \\
\text{MWI} & \quad 1-2 \text{ min.} \\
\end{align*}
\]

HDNIB = [hydroxy - (2,4-dinitrobenzenesulfonyloxy) iodo] benzene

Author claims here that the use of HTI in place of HDNIB, for the above reaction, provides oxazole in reasonably low yields. This is attributed to the good leaving ability of -ODNs compared to -OTs group.
3] Present Work

A convenient method for the synthesis of substituted oxazoles involving oxidative addition of 1,3-dicarbonyl compounds to aromatic nitriles in the presence of diacetoxyiodobenzene is described.

\[
\begin{align*}
\text{PhI(OAc)}_2 & \quad \text{Ph} \\
+ & \quad \text{CH}_3\text{CN, }0\ ^\circ\text{C} \\
\text{O} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

We had chosen the reaction of dimedone with benzonitrile as a model reaction for this oxidative addition. Experimentally diacetoxyiodobenzene (2 mmol) was added to a stirred solution of dimedone (2 mmol) and benzonitrile (1 mmol) in acetonitrile (15 ml) at 0 °C. The corresponding oxazole derivative was obtained in 68 % yield after stirring for 4 hours. The yield was found to be decreased when the reaction was carried out at room temperature.

This oxidative addition of 1,3-dicarbonyl compounds with aromatic nitriles is not so far reported by using single electron oxidant like CAN and Mn(OAc)$_3$. We have attempted the use of CAN (4 mmol) as an oxidant for the reaction between dimedone (2 mmol) at 0 °C as well as at room temperature in acetonitrile solvent. But the reaction did not proceed to oxazole formation.

\[
\begin{align*}
\text{PhI(OAc)}_2 & \quad \text{Ph} \\
+ & \quad \text{CH}_3\text{CN, }0\ ^\circ\text{C} \\
\text{O} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

We have attempted this reaction on the basis of a parallel report on the oxidative addition of dimedone to olefins in presence of CAN.
4] Results and Discussion:

Although several solvents such as methanol, CH₂Cl₂, CHCl₃ and CH₃CN has been reported for diacetoxyiodobenzene, we have ambiguously chosen acetonitrile as a solvent for the reaction. Very surprisingly, no oxazole formation has taken place from solvent CH₃CN participation in the reaction.

The general attributes of the methodology were studied by a panel of representative β-dicarbonyl compounds and aromatic nitriles containing various functional groups. The results are summarized in Table 1.

The reaction between dimedone and aromatic nitriles containing electron donating to withdrawing groups have been studied (entries 1 to 6). The yields of oxazole formation was found to be more with electron releasing substituent on nitrile (entries 2, 4 and 5). The electron withdrawing group like –NO₂ gives oxazole in a reasonably low yield (entry 6). These finding support our proposed mechanism with intermediacy of carbocation 5 (page no). In other words, the electron releasing groups stabilises carbocation 5 while electron withdrawing groups destabilizes the same. So the yields of the reaction varies accordingly.

The reaction of dimedone with p-hydroxybenzonitrile was found to be very vigorous. There was formation of pale yellow colour of the reaction mix within 5 minutes. However, the optimum reaction conditions of this protocol give intractable products with the expected formation of iodobenzene. This may be partially attributed to the susceptibility of phenolic oxidation by diacetoxyiodobenzene according to following scheme.

\[
\begin{align*}
\text{HO} &\quad \text{OAc} \\
\text{C=N} &\quad \text{I-OAc} \\
\text{C=O} &\quad \text{AcOH} \\
\text{Ph} &\quad \text{-PhI} \\
\text{Intractable product}
\end{align*}
\]
Similar results were obtained with acetylacetone and dimethylmalonate. When the reaction of acetylacetone and benzonitrile with DIB in CH₃CN at 0 °C was carried out, oxazole 7C was formed in 72% yield.
Table 1: Oxidative addition of β-dicarbonyl compounds to aromatic nitriles using iodobenzenediaacetate in CH$_3$CN at 0 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>β-Dicarbonyl compound a</th>
<th>Aromatic nitrile b</th>
<th>Product c</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{O} )</td>
<td>(\text{CN} )</td>
<td>(\text{CN} )</td>
<td>4</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>(\text{O} )</td>
<td>(\text{CN} )</td>
<td>(\text{OMe} )</td>
<td>4.5</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>(\text{O} )</td>
<td>(\text{CN} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(\text{O} )</td>
<td>(\text{CICN} )</td>
<td>(\text{Cl} )</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>(\text{O} )</td>
<td>(\text{CICN} )</td>
<td>(\text{Cl} )</td>
<td>8</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>(\text{O} )</td>
<td>(\text{NO$_2$CICN} )</td>
<td>(\text{NO$_2$} )</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>(\text{O} )</td>
<td>(\text{CN} )</td>
<td></td>
<td>7</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>(\text{O} )</td>
<td>(\text{CICN} )</td>
<td></td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>(\text{O} )</td>
<td>(\text{CN} )</td>
<td>(\text{MeO} )</td>
<td>8</td>
<td>63</td>
</tr>
<tr>
<td>10</td>
<td>(\text{O} )</td>
<td>(\text{OMe-CN} )</td>
<td>(\text{OMe} )</td>
<td>7</td>
<td>67</td>
</tr>
</tbody>
</table>
5] Reaction Mechanism

The plausible mechanism of the reaction is depicted in Scheme 1. The mechanism is initially expected to proceed through the reaction of fairly electrophilic diacetoxyiodobenzene with nucleophilic enol form of 1,3-dicarbonyl compound to form new tricoordinated iodine intermediate 1. This (ligand association/dissociation process) step is supported by several reaction in the literature related to the reaction between enol form of 1,3-dicarbonyl compound and diacetoxyiodobenzene. After the formation of intermediate 1, two different paths A and B are possible for oxazole formation.

Path A :

The tendency of intermediate 1 for the reductive elimination of iodobenzene converts the initial electron rich active methylene carbon to the electron deficient center through umpolung. Taking the advantage of the reductive elimination of iodobenzene, aromatic nitriles are trapped by the intermediate 1 in a crucial C-N bond construction with the formation of a stable carbocation 2.

This mechanistic step is again witnessed by few reactions in the literature making the use of –C=N as a potential nucleophile. Moreover, the relative stability of carbocation 2 is another driving force for C-N bond formation. Then, ring closure occurs with the attack of carboxyl oxygen on the stable carbocation 2 to form C-O bond.

Path B :

The mechanistic path B is rationalized on the basis of tendency of iodine to assemble reacting ligands around its coordination sphere to form crucial C-N bond.

The intermediate 1 can associate nitrile ligand to form intermediate 4 with dissociation of acetate anion. In intermediate 4, the reactive methylene
carbon and nitrogen is attached to iodine, which permits the trapping of carbocation in the C-O bond formation. Then the six membered iodo intermediate 5, expels iodobenzene reductively to form 3.

Finally, acetate anion helps in constructing aromatic oxazole ring 6 with the abstraction of relatively acidic α-H from 3 to carbonyl group of dimedone moiety.
Experimental Section:

Reaction vessels were flame-dried or oven dried and allowed to cool under inert atmosphere for moisture sensitive reactions. All the experiments were initiated at ice temperature under atmospheric conditions.

Purification by column chromatography was done using 100-200 mesh silica gel and appropriate mixture of petroleum ether and ethyl acetate for elution. Commercial grade solvents were used for column chromatography and were distilled before use. Petroleum ether refers to the fraction boiling between 60-80 °C. Analytical thin layer chromatography was performed on glass plates coated with silica gel.

**Typical Procedure:** Diacetoxyiodobenzene (644 mg, 2 mmoles) was at once added to an ice cooled, stirred mixture of β-dicarbonyl compound (2 mmoles) and aromatic nitriles (2 mmoles) in acetonitrile (15 ml). This mixture was stirred for the time as mentioned in Table 1. In most of the cases, the faint yellowish color appear after some time. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was diluted with water (30 ml) and extracted with chloroform (2 x 25 ml). The combined organic extracts were dried over anhydrous sodium sulphate and the solvent was evaporated off. The residue obtained was subjected to chromatography on silica gel column using appropriate percentage combination of petroleum ether and ethyl acetate as elutant to afford the oxazole derivative as the final product.

The iodobenzene isolated during column chromatography was collected and used further for different purposes.
7] Characterization:

IR spectra were recorded on a Perkin Elmer 137-E spectrometer. The \(^1\)H NMR spectra were recorded on a Bruker 300 MHz instrument and the chemical shifts were reported with TMS as an internal standard. Relevant spectral data of some of the compounds are given below.

1] \(^1\)HNMR: \(\delta\) 1.0 (6H, s)

\begin{align*}
&2.3 (2H, s) \\
&2.5 (2H, s) \\
&7.0 (1H, m) \\
&7.2 (2H, m) \\
&7.4 (2H, m)
\end{align*}

IR (cm\(^{-1}\), Neat): 3011, 2987, 2856, 1628, 1592, 1429, 1358, 1210, 1117, 770

Elemental analysis:

Theoretical: C, 74.68; H, 6.22; N, 5.80
Found: C, 74.64; H, 6.19; N, 5.79

Melting Point 172 °C

2] \(^1\)HNMR: \(\delta\) 1.2 (6H, s)

\begin{align*}
&2.5 (2H, s) \\
&2.7 (2H, s) \\
&7.4 (2H, d) \\
&7.6 (2H, d)
\end{align*}

IR (cm\(^{-1}\), Neat): 3009, 2962, 2847, 1702, 1620, 1578, 1353, 1246, 760

Elemental analysis:

Theoretical: C, 65.33; H, 5.08; N, 5.08; Cl, 12.88
Found: C, 65.31; H, 5.09; N, 5.06; Cl, 12.84

Melting Point 138 °C
8] Merits of the Methodology and Conclusion

1. Mild reaction conditions.

2. Side product iodobenzene can be recycled for fresh preparation of diacetoxyiodobenzene.


4. Easy reaction work up.

5. Most of the oxazole formation method requires the separate preparation of starting materials like diazodicarbonyl compounds, 2-acylaminoketone, etc. But this protocol does not require a separate preparation of starting materials.

Conclusion:

We have developed, simple and high yielding access to the oxazole ring using diacetoxyiodobenzene. This methodology should be widely applicable to the preparation of relevant pharmaceutical drugs containing 2,4,5-trisubstituted oxazole ring.
Acquisition Time (sec) 2.5166  Comment Ravi RAP-1 in CDC13  Date

Frequency (MHz) 500.13  Nucleus 1H  Original Points Count 16384  Points Count 16384  Sweep Width (Hz) 6510.42

Temperature (grad C) 0.000

Chloroform-d

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Annotation No. 1 Chloroform-d 7.25
References:


