After characterizing the structures of nitroketones 19(a-f), we used them to convert to their corresponding 2-acetyl and 2-benzoyl indoles. Here the substrates 19(a-f) were treated with two equivalent of triphenyl phosphine and heated at 180° in diphenyl ether. In each of these reactions, the time required for the conversion was 8 hours. The workup of reactions were carried out by initially distilling off diphenyl ether and then the residue obtained was chromatographed using appropriate solvent system. Recrystallisation of the solid obtained gave pure compounds whose structures were characterised by comparison with the products obtained by one pot method i.e, IR superimposability, co-TLC, also the similarity of the melting point. The results with respect to yields obtained are given below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 (b-f)</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>52</td>
</tr>
<tr>
<td>c</td>
<td>42</td>
</tr>
<tr>
<td>d</td>
<td>48</td>
</tr>
<tr>
<td>e</td>
<td>52</td>
</tr>
<tr>
<td>f</td>
<td>44</td>
</tr>
</tbody>
</table>

Once we obtained 2-acetyl indole in sizeable amount, we turned on to our plan described earlier (Scheme XXX). We mixed 2-acetyl indole with phosphorane 11 under variety of condition by changing solvent from toluene, xylene to diphenyl ether, adding benzoic acid as catalyst, it failed to deliver any results. We also tried neat heating of the reactants but here too reaction failed to take place. Even microwave condition failed to give the expected result.
1.5 Present work directed towards synthesis of carbazole ring system

Since we failed to synthesize carbazole precursor to ellipticine, we tried to attempt synthesis of carbazoquinocin (7a) from 2-acetyl indole. Our plan for synthesizing carbazoquinocin was as follows (Scheme XXXXI).

Here the first step was to react 2-acetyl indole with diethyl succinate under Stobbe condensation. When we tried this reaction it failed to give Stobbe product.

We tried to use Wittig-Horner reaction as it is known to give better yield (Scheme XXXXII).
However, again we failed to get the product. So, it was thought that may be exchangeable hydrogen on indole nitrogen may be causing failure. So, it was decided to protect as its benzylsulphonyl amide. This attempt also did not yield any result. Further, work is needed to be done particularly using Emmons reaction.
1.6 CONCLUSION

1) We were able to demonstrate that stable Wittig reagent could be used for the synthesis of carbazole precursor to olivacine. Thereby, it constitutes a formal synthesis of olivacine. However, we could not extend it for the synthesis of ellipticine.

2) A convenient method for the synthesis of 2-acyl and 2-benzoyl indoles has been developed.
1.7 EXPERIMENTAL

**Expt. 1.1 Preparation of triphenyl-α-ethoxycarbonylmethylene phosphorane**

\[ \text{PPh}_3 + \text{BrCH}_2\text{COOEt} \rightarrow \text{PPh}_3\text{CH}_2\text{COOEt} \]

**Expt. 1.2 Preparation of carboethoxy-(α-allyl)-methyldene triphenyl phosphorane (11)**

\[ \text{Ph}_3\text{P} = \text{CHCH}_2\text{COOEt} \]
Expt. 1.3  **Preparation of 3-Formyl indole (10a)**

\[
\text{9a} \xrightarrow{\text{DMF, POCl}_3} \text{10a}
\]

Expt. 1.4  **Preparation of ethyl-[2-allyl-3-(3'-1H-indoly1) propeonate (12)**

\[
\text{10a} \xrightarrow{\text{PPh}_3\text{=C-COOEt}} \text{12}
\]

Expt. 1.5  **Preparation of 2-ethoxycarbonyl-4-methylcarbazole (13)**

\[
\text{12} \xrightarrow{10\% \text{Pd/C}, \text{Ph}_3\text{O}} \text{13}
\]
Expt. 1.6  **One pot preparation of 2-ethoxycarbonyl-4-methylcarbazole (13)**

\[
\begin{align*}
\text{PhS0}_2\text{C1} & \quad \text{H} \\
\text{COOEt} & \quad \text{COOEt}
\end{align*}
\]

\[
\begin{align*}
\text{Pd/C, Ph}_2\text{O, reflux} & \\
\text{10a} & \quad \text{13}
\end{align*}
\]

Expt. 1.7  **Preparation of N-tosylindole (10b)**

\[
\begin{align*}
\text{PhS0}_2\text{Cl} & \\
\text{9a} & \quad \text{10b}
\end{align*}
\]

Expt. 1.8  **Preparation of N-tosyl-3-acetylindole (10d)**

\[
\begin{align*}
\text{Ac}_2\text{O} & \quad \text{anhy AlCl}_3 \\
\text{9b} & \quad \text{10d}
\end{align*}
\]
Expt. 1.9  **Preparation of triphenyl-α-acetyl methylene phosphorane (18a)**

\[
\begin{align*}
\text{ClCH}_2\text{COCH}_3 & \quad \xrightarrow{\text{PPh}_3} \quad \text{Ph}_3\text{P} \equiv \text{CH}_2\text{COCH}_3 \\
\text{dry benzene} & \quad \text{Cl} & \quad \text{NaOH} \\
\text{Ph}_3\text{P} \equiv \text{CHCOCH}_3 & \quad 18a
\end{align*}
\]

Expt. 1.10  **Preparation of 4-[2'-nitrophenyl]-3-buten-2-one (19a)**

\[
\begin{align*}
\text{CHO} + \text{Ph}_3\text{P} \equiv \text{CHCOCH}_3 & \quad \xrightarrow{\text{MeOH}} \quad \text{CH}_3 \\
\text{NO}_2 \quad \text{17a} & \quad \text{18a} & \quad \text{19a}
\end{align*}
\]

Expt. 1.11  **Preparation of 2-acetyl indole (20a)**

\[
\begin{align*}
\text{CHO} & \quad \xrightarrow{2 \text{eq PPh}_3} \quad \text{Ph}_3\text{O, reflux} \\
\text{NO}_2 & \quad \text{19a} & \quad \text{20a}
\end{align*}
\]
**Expt.1.12 One pot preparation of 2-acetyl indole (20a)**

![Chemical structure of 2-acetyl indole](image1)

**Expt.1.13 Preparation of 4,5-methylenedioxy-2-nitrobenzaldehyde (17b)**

![Chemical structure of 4,5-methylenedioxy-2-nitrobenzaldehyde](image2)

**Expt.1.14 Preparation of 4,5-dimethoxy-2-nitrobenzaldehyde (17c)**

![Chemical structure of 4,5-dimethoxy-2-nitrobenzaldehyde](image3)
Expt.1.15  One pot preparation of 2-acetyl-5,6-methylenedioxy indole (20b)

Expt.1.16  One pot preparation of 2-acetyl-5,6-dimethoxy indole (20c)
Expt. 1.17 Preparation of bromoacetyl benzene/bromoacetophenone

Expt. 1.18 Preparation of triphenyl-α-benzoyl methylene phosphorane (18b)

Expt. 1.19 One pot preparation of 2-benzoyl indole (20d)
Expt.1.20  One pot preparation of 2-benzoyl-5, 6-methylenedioxy indole (20e)

Expt.1.21  One pot preparation of 2-benzoyl-5, 6-dimethoxy indole (20f)

Expt.1.22  Preparation of 4,5-methylenedioxy-2-nitro-3-buten-2-one (19b)
Expt 1.23 Preparation of 4,5-dimethoxy-2-nitro-3-buten-2-one (19c)

Expt 1.24 Preparation of 3-(2'-nitrophenyl)-1-phenyl-2-propenone (19d)

Expt. 1.25 Preparation of 3-(2'nitro-4',5'-methylenedioxy)-1-phenyl-2-propenone (19e)
Expt. 1.26 Preparation of 3-(2'-nitro-4',5'-dimethoxy)-1-phenyl-2-one (19f)

Expt. 1.27 Preparation of 2-acetyl-5,6-methylenedioxy indole (20b)

Expt. 1.28 Preparation of 2-acetyl-5,6-dimethoxy indole (20c)
Expt. 1.29 Preparation of 2-benzoyl indole (20d)

Expt. 1.30 Preparation of 2-benzoyl-5,6-methylenedioxy indole (20e)

Expt. 1.31 Preparation of 2-benzoyl-5,6-dimethoxy indole (20f)
**Expt. 1.1 Preparation of triphenyl-α-ethoxycarbonyl methylene phosphorane**

Addition of a solution of triphenyl phosphine (15.7g, 60mmol) in dry benzene (30ml) to a solution of ethylbromoacetate (11.7g, 60mmol) in dry benzene (10ml) at room temperature, resulted in an elevation in temperature to about 70°C and the precipitation of a salt. After allowing the mixture to cool to room temperature, it was vigorously shaken and left overnight. The separated solid was filtered, washed with dry benzene and dried.

The stirred solution of the above salt in water (150ml) and benzene (100ml) was neutralised by aqueous sodium hydroxide to a phenolphthalein end point. The benzene layer was separated, dried (anhy. Na₂SO₄) and concentrated to about 1/3rd volume. Addition of n-hexane (40-60°C) resulted in the separation of the crystalline product which was filtered and dried to afford triphenyl-α-ethoxycarbonylmethylene phosphorane (14.6g, 70%) m.p.125-126°C (lit.83 m.p. 125-127°C).

**Expt. 1.2 Preparation of carboethoxy-(α-allyl)-methylidene triphenyl phosphorane (11)**

A mixture of allyl bromide (25ml) and carboethoxymethylene triphenyl phosphorane (10g, 2.87mmol) was refluxed for 5 hours and kept overnight. It was filtered and the solid obtained was washed with dry ether. On recrystallisation from chloroform+pet.ether it furnished salt (8.1g, 60%) m.p.150-151°C. The above salt was dissolved in water (125ml) and benzene (100ml) was added to it. Phenolphthalein (1 or 2 drops) was added to it. Sodium hydroxide solution (10N) was added to it with stirring till the pink colour persisted. The benzene layer was separated and the aqueous layer was extracted with benzene (50ml). The combined benzene layer was dried.
dichloromethane:n-hexane (1:9) furnished pure white crystals as product 10b (1.4g, 81.85%) m.p. 75°C (lit. m.p. 75-79°C).

Expt. 1.8 Preparation of N-tosyl-3-acetylinole (10d)

A stirred suspension of Aluminium chloride (0.83g, 6.2mmol) in dry CH₂Cl₂ (17ml) under pressure was slowly treated with acetic anhydride (0.679ml, 6.6mmol). The solution was stirred at room temperature for 0.25hr. and then treated with a solution of 1-phenyl sulphonylindole (10b) (0.75g, 3.1mmol) in dry dichloromethane (10ml). The mixture was stirred for 0.5hr. poured over crushed ice (50g) and and extracted with dichloromethane (3x125ml). The combined organic extracts were then washed with brine (250ml), saturated aqueous sodium bicarbonate (250ml) & brine (250ml) dried over potassium carbonate & concentrated in vacuum. The crude product was recrystallised using methanol (0.434g, 45%) m.p. 153°C (lit. m.p. 155°C)

Expt. 1.9 Preparation of triphenyl-α-acetyl methylene phosphorane (18a)

Addition of a solution of triphenylphosphine (14.1g, 50mmol) in dry benzene (5ml) to a solution of chloroacetone (5g, 50mmole) in dry benzene (5ml) at room temperature. The reaction mixture was vigorously shaken and left overnight. The separated solid was filtered, washed with dry benzene and dried.

The stirred solution of the above salt in water (10ml) and benzene (15ml) was neutralised by aq. sodium hydroxide to a phenolphthalein end point. The benzene layer was separated, dried over anhy.Na₂SO₄ & concentrated (to about 1/3rd volume). Crystalline product was obtained by addition of n-hexane, which was filtered &
dried to afford triphenyl-α-acetyl methylene phosphorane (3.32, 80%). m.p.205 °C (lit.80 m.p.205-206 °C).

**Expt.1-10 Preparation of 4-([2'-nitrophenyl]-3-buten-2-one (19a)**

A mixture of 2-nitrobenzaldehyde (2.0g, 13.2mmol) and phosphorane 18a (4.11g, 13mmol) in methanol (15ml) was refluxed for two hours. Methanol was removed on water bath and the residue was chromatographed over silicagel using ethylacetate:pet.ether (1:9) as an eluent. Solid obtained was recrystallised using methanol, 19a (2.02, 80%) m.p.54°C (lit.75 m.p.56-57°C).

**Expt.1-11 Preparation of 2-acetyl indole (20a)**

Compound 19a (1g, 5.2mmol) with triphenyl phosphine (3.01g, 11.5mmol) was heated in diphenylether (5ml) at 180°C for 2 hrs. Chromatography over silica gel using ethyl acetate: pet.ether (3:7) as eluent furnished solid, which was recrystallised using dichloromethane:pet.ether (5:5) (0.474g, 57%) m.p.152°C (lit.76 m.p. 152°C).

**Expt.1-12 One pot preparation of 2-acetyl indole (20a)**

Compound 17a (0.5g, 3.3mmol), phosphorane 18a (1.05g, 3.3mmol) and triphenyl phosphine (1.73g, 6.6mmol) was refluxed in diphenylether (5ml) for 2 hrs. Diphenyl ether was distilled under vacuum. Chromatography over silica gel using ethyl acetate:pet.ether (3:7) as eluent furnished solid, which was recrystallised using dichloromethane:pet.ether (5:5) (0.247g, 48%) m.p.152°C (lit.76 m.p. 152°C)
Expt.1.13 **Preparation of 4,5-methylenedioxy-2-nitrobenzaldehyde (17b)**

4,5-methylenedioxybenzaldehyde (2.0g, 13mmol) was heated with conc.nitric acid (15ml) at 60°C for about 15-20mins. time duration. Then the reaction mixture was poured into crushed ice pieces with constant stirring. Yellow coloured precipitate separated out, which was filtered and recrystallised using ethyl alcohol (1.71g, 66%) m.p.90°C (lit.77m.p.88°C).

Expt.1.14 **Preparation of 4,5-dimethoxy - 2-nitrobenzaldehyde (17c)**

Followed the same procedure as expt.1.13, yield (1.75g, 69%), m.p.129°C (lit.78m.p.128-133°C).

Expt.1.15 **One pot preparation of 2-acetyl-5,6-methylenedioxy indole (20b)**

Followed the same procedure as expt.1.12, yield (0.09g, 43.22%), m.p.170°C.

Expt.1.16 **One pot preparation of 2-acetyl-5,6-dimethoxy indole (20c)**

Followed the same procedure for preparation as expt.1.12, yield (0.07g, 36%), m.p.148°C.
**Expt.1.17 Preparation of bromoacetyl benzene/bromoacetophenone**

Bromine (1.95ml) was added dropwise to a stirred solution containing acetophenone (7.5g, 60mmol) and a drop of 48% hydrobromic acid in 50ml of glacial acetic acid in an ice bath. The rate of addition was adjusted so that the temperature never exceeds 20°C. After the addition, stirring was continued for 30 mins. at room temperature.

Calculated 1ml of the solution was withdrawn and crystallised by scratching with a glass rod, while the remaining solution was cooled to 3-4°C. The seed crystals were added, whereupon phenacyl bromide precipitated out of solution. The colourless crystals were collected by filtration, washed several times with a total of 30ml of ethanol/water (1:1) and dried in vacuum. The yield was (5.9g, 47.44%) m.p.47°C (lit.79 m.p.47-48°C).

**Expt.1.18 Preparation of triphenyl-α-benzoyl methylene phosphorane (18b)**

Addition of a solution of triphenylphosphine (6.55g, 25mmol) in dry benzene (5ml) to a solution of bromoacetophenone (5.0g, 25mmol) in dry benzene (5ml) at room temperature. The reaction mixture was vigorously shaken and left overnight. The separated solid was filtered, washed with dry benzene and dried.

The stirred solution of the above salt in water (10ml) and benzene (15ml) was neutralised by aq.sodium hydroxide to a phenolphthalein end point. The benzene layer was separated, dried over anhy.Na₂SO₄ & concentrated (to about 1/3rd volume). Crystalline product was obtained by addition of n-hexane, which was filtered & dried to afford triphenyl-α-benzoyl methylene phosphorane (4.5, 47.8%) m.p.181°C (lit.80 m.p.181-182°C)
Expt.1.19  **One pot preparation of 2-benzoyl indole**  
(20d)

Compound 17a (0.5g, 3.3mmol), phosphorane 18b (1.25g, 3.3mmol) and triphenyl phosphine (1.73g, 6.6mmol) was refluxed in diphenylether (5ml) for 2 hrs. Diphenyl ether was distilled under vacuum. Chromatography over silica gel using ethyl acetate:pet.ether (3:7) as eluent furnished solid, which was recrystallised using dichloromethane:pet.ether (5:5) (0.21g, 48.5%) m.p.147°C (lit.70 m.p. 151-152°C)

Expt.1.20  **One pot preparation of 2-benzoyl-5,6-methylenedioxy indole** (20e)

Followed the same procedure as expt.1.19, yield (0.06g, 30%), m.p.200°C.

Expt.1.21  **One pot preparation of 2-benzoyl-5,6-dimethoxy indole** (20f).

Followed the same procedure as expt.1.19, yield (0.08g, 30%), m.p. 180°C (lit.81 m.p. 176-178°C).

Expt.1.22  **Preparation of 4,5-methylenedioxy-2-nitro-3-buten-2-one** (19b)

4,5-methylenedioxy-2-nitrobenzaldehyde (1.0g, 5.1mmol) was refluxed with phosphorane 18a (1.63, 5.1mmol) in methanol (5ml) for two hours. Solid separated on keeping overnight was filtered, washed with little methanol & dried. Recrystallisation using methanol furnished pure product 19b (1.04g, 86%) m.p.160°C.
Expt 1.23  **Preparation of 4,5-dimethoxy-2-nitro-3-butene-2-one** (19c)

Followed the same procedure as expt.1.22, yield (1.0g, 84%), m.p. 168°C (lit.82 m.p. 172°C).

Expt. 1.24  **Preparation of 3-([2'-nitrophenyl]-1-phenyl-2-propenone** (19d)

Followed the same procedure as expt.1.22, using phosphorane 18b yield (2.25g, 67%), m.p. 126°C (lit.73 m.p. 127-128°C).

Expt. 1.25  **Preparation of 3-([2' nitro-4',5']methylenedioxy]-1-phenyl-2-propenone** (19e)

Compound 17b (0.5g, 2.5mmol) was refluxed with phosphorane 18b (0.97g, 2.5mmol) in methanol (10ml) for 2 hours and kept overnight. The solid separated was filtered and dried. Recrystallisation using methanol gave pure product 19e (0.575g, 75.5%) m.p. 154°C.

Expt. 1.26  **Preparation of 3-([2' nitro-4',5'-dimethoxy]-1-phenyl-2-one** (19f)

Followed the same procedure as Expt.1.25, yield (0.461g, 62%), m.p. 180°C (lit.81 m.p. 182-183°C).
Expt. 1.27 **Preparation of 2-acetyl-5,6-methylenedioxy indole (20b)**

Compound 19b (0.5g, 2.1mmol) was heated with triphenyl phosphine (1.22g, 4.6 mmol) in diphenyl ether (5ml) at 180°C for 8 hours. The reaction mixture on cooling was chromatographed using ethylacetate:pet.ether (3:7) as eluent furnished product 20b (0.224g, 52%) m.p.170°C.

Expt. 1.28 **Preparation of 2-acetyl-5,6-dimethoxy indole (20c)**

Followed the same procedure as Expt. 1.27, yield (0.183g, 42%), m.p.148°C.

Expt. 1.29 **Preparation of 2-benzoyl indole (20d)**

Followed the same procedure as Expt. 1.27, yield (0.170g, 48.5%), m.p.147°C (lit. m.p.151-152°C).

Expt. 1.30 **Preparation of 2-benzoyl-5,6-methylenedioxy indole (20e)**

Followed the same procedure as expt.1.27, yield (0.095g, 52.40%), m.p.200°C.

Expt. 1.31 **Preparation of 2-benzoyl-5,6-dimethoxy indole (20f)**

Followed the same procedure as expt.1.27, yield (0.08g, 44.5%), m.p.181°C.
1.8 REFERENCES


CHAPTER - II
SYNTHETIC STUDIES IN ISOXAZOLES

2.1 Introduction

Isoxazoles\(^1\) (1), represent an important class of oxygen heterocycles. It has potent biological activity. Isoxazoles have been used for the synthesis of intermediates of various natural products. They act as building blocks for construction of new molecular systems\(^2\).

\[
\begin{array}{c}
\text{R}^2 \\
\text{N} \\
\text{O} \\
\text{R}^1
\end{array}
\]

Various isoxazole derivatives are known to exhibit diverse biological activity. Among these, ABT-418\(^3\) (2), (S)-3- methyl-5- (1-methyl-2- pyrrolidinyl) isoxazole represents a new class of isoxazole acting as cholinergic channel activators. Such an activator has been evaluated as a safe and effective treatment for Alzheimer's disease, related personality changes and memory loss. Similarly, isoxazole derivative (3), is an antihypertensive sulphonamide\(^4\). Isoxazole carboxamides\(^5\) and 4-benzoyl isoxazoles\(^6\) both act as herbicides for controlling the growth of weeds.
Monoamine oxidase inhibitor, α-S, 5S-α-Amino-3-chloro-4,5-dihydro-5-isoxazole acetic acid is found to induce differentiation in tumour cells. Isoxazole compounds have also been used as agrochemicals and fungicides. Carbiniloyl isoxazole is an effective anti-inflammatory agent. 3-aryl-5-alkyl isoxazole-4-carboxylic acid derivatives are known to act as endoparasiticides. Isoxazole derivatives like 2-(3-arylisoxazol-5-yl) benzoic acid have attracted pharmaceutical & agricultural industries. They also find use as herbicidal and plant growth regulator. Muscimol has powerful psychotropic effects due to its activity in brain nerve cells. They also find use in pharmaceuticals, agrochemicals, semiconductors and polymers. Compound, an isoxazole fused derivative is a potential analgesics while 5-substituted -4-isoxazole acetic acids are also known to exhibit analgesic activity. 3-Methyl-5-pyridinyl isoxazole is an agent for lowering blood sugar levels.
Other uses of isoxazole derivatives lies as improved fluorescent probes for studying natural and synthetic lipid membranes and related areas\textsuperscript{14}. 
2.2 Synthesis of ABT-418

As mentioned above various isoxazole derivatives possess diverse biological activities. We were attracted by ABT-418 (2), a novel cholinergic agent. So far three syntheses of this compound have been reported in literature. The first synthesis involves the original route shown in Scheme I, Wherein eight steps are used for the transformation from L-proline. The important step in this route involves construction of isoxazole moiety via a [3+2] nitrile oxide dipolar cycloaddition.3a.
R.L. Elliot & coworkers\textsuperscript{3b} have successfully reported a second approach (Scheme II) involving four steps starting from L-proline. Here the main step is the addition of dianion of acetoneoxime to N-methyl-methyl ester of L-proline.

\begin{center}
\begin{tabular}{c}
h\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \end{tabular}
\end{center}

\begin{center}
\begin{tabular}{c}
\textbf{Scheme II}
\end{tabular}
\end{center}

The third approach by S.J. Wittenberger synthesizes\textsuperscript{3c} ABT-418 from L-proline in six steps as depicted in Scheme III. In this route the conversion to the final molecule is afforded by treatment of methyl enamino ketone (b) with hydroxylamine hydrochloride to regioselectively produce the ketoxime. The final step involves cyclodehydration of this ketoxime by adding aqueous sulphuric acid and on gentle heating.
All three approaches require strongly basic conditions, for example for the formation of acetylene, n-BuLi is used in the first approach, while in the second and third approach lithium dianion of acetone oxime and sodioacetonitrile respectively is required. Use of such highly basic conditions may lead to racemisation during large scale synthesis. Also in the second and third approach reaction of condensation of the proline ester has to be done carefully as the product formed is a ketofunction which is more reactive than the starting ester function for a nucleophile attack. In view of this, we thought of devising a milder approach.
Our retrosynthetic analyses of ABT-418 is depicted in Scheme IV

The first step in the approach was to prepare $\alpha,\beta$-unsaturated ketone or the corresponding oxime from protected or N-methyl prolinal. This would have been possible by a reaction between phosphorane and the carbonyl group of the prolinal. The last step required oxidative addition of the oxime to lead to isoxazole directly.

So, it was necessary to know the literature methods utilised for the synthesis of isoxazoles to check whether such an approach is reported for the synthesis of isoxazole.
2.3 Synthesis of Isoxazoles

Kochetkov and Sokulov\textsuperscript{15} in their review in 1963 have reported various routes towards synthesis of isoxazoles. The isoxazole ring has 3 carbon atoms, one oxygen and one nitrogen in its five-membered structure. Accordingly, the synthetic routes towards isoxazoles may be classified (given below) i.e. according to the number of isoxazole ring atoms in each component system. Presently various developments have been made in the synthesis.

A] (3+2) routes \([C-C-C + N-O]\) & \([C-N-O + C-C]\)
B] (4+1) routes \([C-C-C-N + O]\), \([C-C-N-O + C]\) & \([C-C-C-O + N]\)
C] (3+1+1) route
D] (2+2+1) route
E] (5+0) routes \([C-C-C-N-O]\)

\textbf{Route A}

This route involves three carbon atoms added to NO unit. Usually 1,3-dicarbonyl system i.e. 1,3-diketone or ketoaldehyde form the CCC unit. Sometimes β-substituted vinylketones, α, β-acetylenic ketones are also used. The NO unit is always hydroxylamine. Another combination is carbon, nitrogen, & oxygen unit joined to C-C unit.

Here CCC unit forms a part of the ring with attack by hydroxylamine leading to a labile acyclic intermediate which recyclises to form an isoxazole. The most useful method for the preparation of isoxazoles is the cyclocondensation of easily available materials 1,3-diketones with hydroxylamine\textsuperscript{16} (Scheme V).
It's limitation lies in the fact that it lacks real control over the regioselectivity. Kamihiko Mizuno & coworkers\textsuperscript{17a} have reported a method wherein NO is inserted into cyclopropane ring using two moles of nitrosonium salt NOBH\textsubscript{4}. This methodology is also shown for use of 1,2-diaryl cyclopropane for the synthesis of 3,5-diarylisoaxazoles. Recently, Saginova et al\textsuperscript{17b} have reported such reaction using sodium nitrite in trifluoroacetic acid (Scheme VI).

Isoxazole has also been synthesized by replacing hydroxylamine with dinitrogentrioxide & reacting it with $\alpha$, $\beta$-unsaturated ketones\textsuperscript{18} (Scheme VII).
J.B. Carr & coworkers\textsuperscript{19} have reported a method wherein oximation of 1,3-diketone followed by cyclisation on heating in presence of acetyl chloride furnishes isoxazole in 67\% yield (Scheme VIII).

\beta\text{-ketoaldehyde on treatment with hydroxylamine in presence of sodium acetate buffer has been reported to give 3 \& 5 monosubstituted isoxazoles\textsuperscript{20} (Scheme IX).
Elnagdi & coworkers$^{21}$ have carried out cyclisation of arylhydrazone in presence of varied basic conditions (Scheme X).

An intramolecular cycloaddition has been reported wherein propagyl ether is constrained to give 4-substituted isoxazole$^{22}$ (Scheme XI).
Nitrile oxides are known to react with appropriate alkynes giving 5-substituted, 4-acyl-5-substituted\textsuperscript{23}, and 4 \& 5 substituted isoxazoles\textsuperscript{24}. Various substituted alkene aromatic systems have been reported to be used for the synthesis of isoxazoles by reacting with nitrile oxides\textsuperscript{25} (Scheme XII).

\[
R\text{-CNO} + R'\text{-CH=CHX} \xrightarrow{-HX} \begin{array}{c}
\text{R} \\
\text{N} \\
\text{O} \\
\text{H}
\end{array}
\]

\textbf{Scheme XII}

A route consisting of 1,3-dipolar cycloaddition of aromatic nitrile oxides to 3-methylnaphthalide have also been reported\textsuperscript{10a} (Scheme XIII).

\[
\begin{array}{c}
\text{Cl} \\
\text{Ar-C=NOH} \\
\text{Et$_3$N, ether}
\end{array}
\xrightarrow{\text{Cl}} \begin{array}{c}
\text{COOH}
\end{array}
\]

\textbf{Scheme XIII}

Recently E. Dominguez et al have reported a novel synthesis of 4,5-diarylisoxazoles\textsuperscript{2a} (Scheme XIV).
Route B

This involves CCNO unit joining another C unit. Nitrosyl chloride addition compounds have been subjected to nucleophilic attack. M. Dines & coworker have reported use of cyano anion as nucleophile for the synthesis of isoxazoles\textsuperscript{26} (Scheme XV).

P. Bravo and C. Ticozzi\textsuperscript{27} have employed dimethyl sulphide of acetophenone as attacking agent for the same purpose (Scheme XVI) also use of dimethyl sulphone of toluene has been reported as a nucleophile\textsuperscript{28} (Scheme XVII).
Demina et al\textsuperscript{29} have reported a method wherein 3,5-diarylisoxazoles have been synthesized using nitroacetophenone oxime and benzaldehyde in the presence of base (Scheme XVIII).

Acetophenone oxime on treatment with 2 equivalents n-BuLi, followed by treatment with cyanobenzene (benzonitrile) has been reported to give 3,5-diarylisoxazoles\textsuperscript{30}, while $\alpha$-substituted lithium dianion of acetophenone oxime with esters or amides gives 3,4,5-trisubstituted isoxazoles\textsuperscript{31} (Scheme XIX).
Synthesis involving [CCCO + N] addition has also been employed\textsuperscript{32} (Scheme XX).

\[
\text{Route C}
\]

The route involving (3+1+1) pathway has been less established\textsuperscript{33}. The former involves condensation of nitro compounds in presence of base.

Several routes involving ring transformations of other heterocyclic compounds to isoxazoles have been reported. Although theoretically several transformations involving oxazoles, acylaziridines etc. have been reported, practically their use is not established.

Well known among them is the ring contraction of condensed 4-pyrones in the synthesis of steroidal isoxazoles\textsuperscript{34,35}. As isoxazolines are known to give isoxazoles, routes involving ring transformations to isoxazolines are known such as ring expansion of oxiranes\textsuperscript{36} and oxetanones\textsuperscript{37}, ring contraction of pyridinium salts, pyrimidinium-N-
oxides, pyrilium salts, ketonylidinepyrans, chromones, thiocromones, chromylum salts, and oxazinones. Photoisomerisation of pyridazine dioxides. Other ring transformations include of pyrrolenines, furans, dithioles, oxaphosphazoles, benzotriazepines.

**Route D**

There seems to be no reports involving this route.

**Route E**

The last route that is described is of (5+0) synthesis. Such reactions involve cyclisation of synthons containing all five ring atoms, usually in the sequence C-C-C-N-O. Such a route provides regiospecificity to great extent. All reactions must involve at some stage cyclisation of a isoxazole ring. Most common is conversion involving α,β-unsaturated oximes. Hansen & Strong have reported a method using N-Bromosuccinimide, While Maeda et al have used palladium complexes for the synthesis of 3,5-diaryl isoxazoles in 80-90% yield. Similarly, lead tetracetate and iodine/sodium bicarbonate have also been used. The former synthesizes 3,5-diaryl isoxazoles in low yields, while the latter is mostly used for the synthesis of aliphatic isoxazoles. Recently, X. Wei. et al have reported the synthesis using TPCD [tetrakis(pyridine)]cobalt(II) dichromate, where alongwith required product some starting chalcones are also recovered. The schemes for the above have been depicted below (Scheme XXI).
Electrochemical reduction of nitroalkene systems has been reported to give 3,4,5-trisubstituted isoxazoles\(^9\) (Scheme XXII).

![Scheme XXII]

Many nitro group containing substrates like \(\alpha,\beta\)-unsaturated diesters\(^60\) (Scheme XXIII), ketones\(^61\) (Scheme XXIV) are known to give 3,5-disubstituted isoxazoles under acidic conditions.

![Scheme XXIII]

Michael addition of alkene oxime to propargyl nitrile followed by hydrolysis has been reported to give 3-amino isoxazole\(^62\) (Scheme XXV).

![Scheme XXIV]
Dioximino compounds also yields isoxazoles (Scheme XXVI).

Cyclisations reactions play an important role in the synthesis of the 3,5- disubstituted isoxazoles. β- Keto oximes under sulphuric acid conditions and in ethanolic HCl yield isoxazoles (Scheme XXVII).

The above reactions involve CCCNO synths with one NOCCC synthon. Examples of OCCCN cyclisations are also rare.
2.4 Present work

Careful examination of literature methods revealed that there are only five methods using the approach (5+0) via α,β- unsaturated oxime. Most of these methods are used for the synthesis of 3,5-diarylisoxazoles. LTA method has reported low yields (24-28%), along with recovery of starting chalcones. Similarly, the method using TPCD complex could not rule the possibility of formation of the starting ketone back in the reaction mixture.

Dichlorodicyanoquinone (DDQ) is a well known oxidising reagent mainly used for aromatisation\(^{65}\). Two reports are available for the oxidative cyclisation of o-hydroxy chalcone to chromone\(^{66}\) and 3-o-hydroxy phenyl coumarins to coumestan\(^{67}\). We thought of using this reagent for oxidative cyclisation of chalcone oximes. Initially, we thought of synthesizing 3,5-diarylisoxazoles, as mentioned earlier that, we were attracted towards ABT-418, which is a 3,5-disubstituted isoxazole. Also 2-(3-aryl-isoxazol-5-yl) benzoic acid derivatives have interesting biological activities\(^{10a}\).

Thus, we decided to test the use of DDQ on chalcone oxime (Scheme XXVIII), which was easily available by Claisen-Schmidt condensation\(^{68}\) between benzaldehyde and acetophenone followed by treatment with hydroxylamine hydrochloride in presence of a weak base. The chalcone oxime was prepared by the known literature method\(^{69}\).
The chalcone oxime obtained was stirred in methanol with two eq. of DDQ at room temperature. After 2 hours tlc indicated absence of the starting chalcone oxime, while two new spots were observed. One of them could be corresponding to isoxazole 9a and the other could be dichlorodicyanohydroquinone. The solvent methanol, was removed at the pump and the residue was chromatographed on silica gel. Initial fractions gave a solid, which on recrystallisation melted at 140°C. In its IR spectrum it showed absence of a peak between 3000-3500 cm\(^{-1}\) indicating that oxime function is absent in the product obtained. Also absence of a peak in the carbonyl region
indicated that there is no recovery of the chalcone in the reaction. In it's PMR (CDCl₃) [Fig.2A] it showed a singlet at 6.84 δ for one proton which could be attributed to C-4 hydrogen of isoxazole nucleus. In the aromatic region a multiplet was seen between 7.2-7.98 integrating for ten protons which could be assigned to the ten hydrogens of the two phenyl groups at 3 & 5 positions. Thus, on the mode of formation and spectral data structure 9a was assigned to the compound. This was further supported by the similarity of it's melting point 140°C with the lit.56,70 m.p.141-142°C. The yield of the product was found to be 75%.
SC1-96-33
OBSERVE 31
FREQUENCY 399.951 MHz
SPECTRAL WIDTH 2000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 1.000 sec
PULSED WIDTH 1.0 usec
AMBIENT TEMPERATURE
NO. REPLICATIONS 32
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 65536
TOTAL ACQUISITION TIME 2.2 min
Nov. 2, 96
Virginia Tech NMR Facility

Fig. 2 A
After the successful synthesis of parent 3,5-diphenyl isoxazole, we thought of checking the generality of this reaction. Initially, we thought of testing it for few substituted diaryl isoxazoles.

Acetophenone was then condensed with pipernal. The product obtained showed carbonyl peak at 1665 cm\(^{-1}\) in its IR spectrum. Its m.p. 120\(^\circ\)C was closely matching with lit.\(^7\) m.p. 122\(^\circ\)C. The structure 7b was suggested. The chalcone 7b was then treated with hydroxylamine using the usual conditions to obtain the oxime, which melted at 140\(^\circ\)C and also showed presence of a band in the hydroxyl region at 3300 cm\(^{-1}\) in its IR spectrum. Based on its mode of formation and spectral (Fig.2B) data structure 8b was assigned to the oxime.
This oxime was then stirred with two eq. DDQ in methanol and kept overnight (monitored by tlc). Chromatographic separation on silica gel gave a compound which has following spectral data.

IR (KBr) : $\nu_{\text{max}}$ 1250 cm$^{-1}$
PMR (CDCl$_3$) :

<table>
<thead>
<tr>
<th>$\delta$</th>
<th>s</th>
<th>2H</th>
<th>-OCH$_2$O-</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.048</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.69</td>
<td></td>
<td>1H</td>
<td>C$_4$-H</td>
</tr>
<tr>
<td>7.2-7.48</td>
<td>m</td>
<td>8H</td>
<td>Ar-H</td>
</tr>
</tbody>
</table>

The mode of formation, spectral data & similarity of it's m.p. 120°C with the lit.$^{72}$ m.p.122-123°C attributed structure 9b for this compound. The yield was found to be 72%.

p-Methoxy acetophenone was then similarly, condensed with benzaldehyde and subjected to oxime formation. Structures for both these compounds obtained were attributed based on it's mode of formation, IR and comparison with the lit.$^{73,74}$ m.p.

<table>
<thead>
<tr>
<th>Structure</th>
<th>IR(KBr) $\nu_{\text{max}}$</th>
<th>m.p.</th>
</tr>
</thead>
<tbody>
<tr>
<td>7c</td>
<td>1650 cm$^{-1}$</td>
<td>100°C (102°C)</td>
</tr>
<tr>
<td>8c</td>
<td>3280 cm$^{-1}$</td>
<td>138°C (140°C)</td>
</tr>
</tbody>
</table>

The oxime 8c was then treated with 2 eq. DDQ in methanol. The reaction was stirred overnight as the reaction reached to completion (monitored by tlc). The residue obtained after evaporation of methanol was column chromatographed on silica gel. The initial fractions gave a solid. The IR and PMR spectral data (given below) [Fig.2C] suggested structure 9c for this compound.
SCT-97-39
OBSERVE HS
FREQUENCY 399.951 MHz
SPECTRAL WIDTH 5000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 3.4 usec
AMBIENT TEMPERATURE
150 REPETITIONS 24
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 65536
TOTAL ACQUISITION TIME 1 minutes
Delay 0.97
Virginia Tech STC NMR Facility

Fig. 2 C
\(\text{IR (KBr) : } v_{\text{max}} 1250 \text{ cm}^{-1}\)

\(\text{PMR (CDCl}_3\):\)

\[
\begin{array}{|c|c|c|c|}
\hline
3.87 & s & 3H & \text{OCH}_3 \\
6.78 & s & 1H & \text{C}_4\text{-H} \\
6.86 & d(6.3 \text{ Hz}) & 1H & \text{Ar-H} \\
7.00 & d(6.3 \text{ Hz}) & 1H & \text{Ar-H} \\
7.2-7.8 & m & 7H & \text{Ar-H} \\
\hline
\end{array}
\]

The structure was further confirmed by its m.p. 120°C, which closely matched with the lit.\textsuperscript{75} m.p. 120°C. The yield of the product was found to be 74%.

p-Methoxy acetophenone was then condensed with anisaldehyde to get the corresponding chalcone 7\textit{d}. The structure of this chalcone showed in its IR spectrum a peak at 1660 cm\(^{-1}\) for \(\alpha,\beta\)-unsaturated ketone and similarity of its melting point 100°C to its lit.\textsuperscript{76} m.p. 101-102°C, further confirmed its structure to be 7\textit{d}. This chalcone was then subjected to usual oxime formation, the structure of it was again suggested by a peak at 3150 cm\(^{-1}\) in its IR spectrum for \(=\text{N-OH}\) function and its m.p. 130°C matching with that of the literature\textsuperscript{74} m.p. 132°C. This chalcone oxime 8\textit{d} was then treated with two eq of DDQ in methanol. The product obtained from this reaction was recrystallised. The mode of formation, its melting point matching with lit.\textsuperscript{17a} m.p. and the spectral data given below suggested structure 9\textit{d} for this compound.

Melting point: 140°C (lit.\textsuperscript{17a} m.p. 141-142°C).
Yield was found to be 64%.

Similarly, p-methoxy acetophenone was condensed with pipernal to get the corresponding chalcone. It melted at 130°C (lit.\textsuperscript{76} m.p.131°C). In it's IR spectrum it showed a band at 1660 cm\textsuperscript{-1} in the carbonyl region for \(\alpha,\beta\)-unsaturated carbonyl and 1250 cm\textsuperscript{-1} in O-C region. The chalcone 7e was then subjected to treatment with hydroxylamine hydrochloride under the usual conditions. The product obtained had melting point of 180°C. It's spectral properties (shown below) indicated structure 8e for this compound.

IR (KBr) : \(\nu_{\text{max}}\) 1510, 1250 cm\textsuperscript{-1}

PMR (CDCl\textsubscript{3}), [Fig.2D]

\[
\begin{array}{|c|c|c|c|}
\hline
\delta & \text{Multiplet} & J & \text{Assignments} \\
\hline
3.86 & s & 6H & 2\times\text{OCH}_3 \\
6.65 & s & 1H & \text{C}_4-\text{H} \\
6.99 & d(J=6.6 \text{ Hz}) & 4H & \text{Ar-}\text{H} \\
7.75-7.8 & m & 4H & \text{Ar-}\text{H} \\
\hline
\end{array}
\]

\[
\begin{array}{|c|c|c|c|}
\hline
\delta & \text{Multiplet} & J & \text{Assignments} \\
\hline
3.85 & s & 3H & \text{OCH}_3 \\
5.97 & s & 2H & \text{OCH}_2\text{O} \\
6.67 & d(J=16.6 \text{ Hz}) & 1H & \text{C}_2-\text{H} \\
6.7-6.9 & m & 4H & \text{Ar-}\text{H} \\
7.4 & m & 3H & \text{Ar-}\text{H} \\
7.51 & d(J=16.6 \text{ Hz}) & 1H & \text{Ar-}\text{H} \\
2.31 & \text{bs} & & \text{OH} \\
\hline
\end{array}
\]

(exchangeable with D\textsubscript{2}O)
The oxime was then stirred with 2 eq. of DDQ in methanol for two hours (monitored by tlc). Usual workup provided a solid melting at 152°C. Its analysis suggests C\textsubscript{17}H\textsubscript{13}NO\textsubscript{4} as its molecular formula. The mode of formation, analysis and spectral data (given below) suggested structure 9e for this compound.

IR (KBr) : \( \nu_{\text{max}} \) 1619 cm\(^{-1}\), 1514 cm\(^{-1}\), 1450 cm\(^{-1}\), 1269 cm\(^{-1}\), 1058 cm\(^{-1}\), 813 cm\(^{-1}\)

Mass m/z : 149(100), 239, 280(4), 295 (M\(^+\), 52)
PMR (CDCl₃) [Fig.2E]

<table>
<thead>
<tr>
<th>δ</th>
<th>Multiplicity</th>
<th>J</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.86</td>
<td>s</td>
<td></td>
<td>3H OCH₃</td>
</tr>
<tr>
<td>6.04</td>
<td>s</td>
<td></td>
<td>2H OCH₂O</td>
</tr>
<tr>
<td>6.63</td>
<td>s</td>
<td></td>
<td>1H C₄-H</td>
</tr>
<tr>
<td>6.88</td>
<td>d(9 Hz)</td>
<td></td>
<td>2H Ar-H</td>
</tr>
<tr>
<td>6.99</td>
<td>d(9 Hz)</td>
<td></td>
<td>2H Ar-H</td>
</tr>
<tr>
<td>7.26-7.78</td>
<td>m</td>
<td></td>
<td>3H Ar-H</td>
</tr>
</tbody>
</table>

$^{13}$C NMR: 55.43, 77.10, 96.39, 101.68, 106.23, 108.88, 114.37, 120.52, 121.74, 121.80, 128.25, 148.3, 149.30, 161.06, 162.64, 169.64.

The yield was found to be 76%.
Spectroscopic Parameters:

- **Frequency:** 300.951 MHz
- **Spectral Width:** 5000 Hz
- **Acquisition Time:** 3.744 sec
- **Relaxation Delay:** 1.880 sec
- **Pulse Width:** 3.4°
- **Ambient Temperature:** No. Repetition No.
- **Double Precision Acquisition:**
- **Data Processing:**
- **FT Size:** 65536
- **Total Acquisition Time:** 3 minutes
- **Sep 9 97**

Additional Information:

- **OBSERVE Hi Frequency:** 399.95 MHz
- **Spectral Width:** 5000 Hz
- **Acquisition Time:** 3.744 sec
- **Relaxation Delay:** 1.880 sec
- **Pulse Width:** 3.4°
- **Ambient Temperature:**
- **Double Precision Acquisition:**
- **Data Processing:**
- **FT Size:** 65536
- **Total Acquisition Time:** 3 minutes
- **Sep 9 97**

Chemical Shift Values:

- **6.5 5.5 5.0 4.5 4.0 3.5 ppm**
  - 0.24 30.20 0.49 45.06 0.03 0.37

**Fig. 2 E**
After synthesizing five 3,5-diarylisoxazoles, we thought of checking the generality of this reaction by changing the substituent at 3 & 5 positions, as we needed to synthesize ABT-418 which is also a 3,5-disubstituted isoxazole. Initially, we opted for preparation of 3-phenyl-5-styrylisoxazole. For this, we required cinnamaldehyde as starting compound. Thus, cinnamaldehyde was condensed with acetophenone to give the corresponding chalcone 7f, the structure was assigned based on its IR spectrum, which showed a band at 1660 cm\(^{-1}\) for carbonyl group of unsaturated ketone and also its similarity of melting point 102\(^{\circ}\)C with the lit.\(^{77}\) m.p. 103-105\(^{\circ}\)C. This was then treated with hydroxylamine to obtain a solid, which melted at 133\(^{\circ}\)C (lit.\(^{78}\) m.p. 135\(^{\circ}\)C). In its IR spectrum it showed a band at 3400 cm\(^{-1}\) for the hydroxyl group of the oxime formed. This oxime 8f obtained was then stirred in methanol with 2 eq. of DDQ for two hours. Usual workup of the reaction mixture gave a solid. The spectral data (given below) of this solid indicated that it may be 3-phenyl-5-styrylisoxazole 9f.

\[
\text{IR(KBr)}: \nu_{\text{max}} 1400 \text{ cm}^{-1}
\]

\[
\text{PMR (CDCl}_3\text{), [Fig.2F]}
\]

<table>
<thead>
<tr>
<th>6.58</th>
<th>s</th>
<th>1H</th>
<th>C(_4)-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.76</td>
<td>d(16 Hz)</td>
<td>1H</td>
<td>CH</td>
</tr>
<tr>
<td>7.01</td>
<td>d(16 Hz)</td>
<td>1H</td>
<td>CH</td>
</tr>
<tr>
<td>7.1-8.0</td>
<td>m</td>
<td>10H</td>
<td>Ar-H</td>
</tr>
</tbody>
</table>

It's melting point 130\(^{\circ}\)C, matched with the lit.\(^{79}\) m.p. 132\(^{\circ}\)C. The yield of the product was found to be 70%. The mode of formation, spectral data & similarity of m.p. with literature m.p. suggested structure 9f for the compound.
OBSERVE H1
FREQUENCY 399.951 MHz
SPECTRAL WIDTH 5000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 3.4 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 24
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 65536
TOTAL ACQUISITION TIME 1 minutes
Sep 9 97
Virginia Tech STC NMR Facility

Fig. 2 F
We then prepared cinnamaldehyde oxime as per literature procedure\textsuperscript{80}. This when subjected to 2 eq. of DDQ in methanol and stirring for 4 hours indicated absence of starting compound (monitored by tlc). Column chromatography over silica gel did not result in isolation of any pure compound.

Similarly, we thought of synthesizing 3-methyl-5-phenyl isoxazole from the corresponding oxime which was prepared by literature procedure\textsuperscript{81}. In this case also under variety of conditions, we failed to get the product. We also prepared the oxime of \(\beta\)-ionone as per literature procedure\textsuperscript{82}. In this case the reaction did not take place at any time and we always recovered the starting oxime.

Thus, we realised that, there is a limitation to the present method of oxidative cyclisation of \(\alpha,\beta\)-unsaturated oxime using DDQ and the requirement is that two aryl groups must be present at 3 & 5 positions.
2.5 Present work towards synthesis of ABT-418

We had simultaneously started our work on the synthesis of isoxazole ABT-418. As per our retrosynthetic analysis depicted in (Scheme IV), we thought of preparing N-methyl prolinal and then condensing it with a stable phosphorane to get an $\alpha,\beta$-unsaturated oxime and cyclise the oxime as per any of the literature$^{54-58}$ method (Scheme XXIX).
Thus, L-proline was treated with ethylchloroformate under basic conditions to get N-carboethoxy prolinol. The structure of it was suggested by the mode of formation, spectral data (given below) and similarity of it's melting point with lit.83 m.p. The yield obtained was 95%.

IR : $v_{\text{max}}$ 3420, 1740, 1675 cm$^{-1}$

PMR: (CDCl$_3$), [Fig.2G]

\[(\delta)\]

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.19-1.34</td>
<td>m</td>
<td>3H</td>
<td>COOCH$_2$CH$_3$</td>
</tr>
<tr>
<td>1.9 -2.24</td>
<td>m</td>
<td>4H</td>
<td>CH$_2$-CH$_2$</td>
</tr>
<tr>
<td>3.38-4.22</td>
<td>m</td>
<td>2H</td>
<td>N-CH$_2$</td>
</tr>
<tr>
<td>4.31-4.4</td>
<td>m</td>
<td>3H</td>
<td>CH &amp;</td>
</tr>
<tr>
<td>4.92</td>
<td>bs</td>
<td>1H</td>
<td>COOCH$_2$CH$_3$</td>
</tr>
</tbody>
</table>

(exchangeable with D$_2$O)
N-carboethoxy proline was then treated with excess of lithium aluminium hydride in ether at room temperature for 3 hours (monitored by tlc). Usual work up gave a liquid. It's IR and PMR spectral data is given below.

IR : \( \nu_{\text{max}} \) 3400 cm\(^{-1}\)
PMR : (CDCl\(_3\))

| 1.66-1.95 | m | 4H | CH\(_2\)CH\(_2\) |
| 2.11-2.4 | m | 5H | N-CH\(_3\), CH\(_2\) |
| 3.0-3.1 | m | 1H | CH |
| 3.43 | dd(2.56 Hz) | 1H | CH-OH |
| 3.65 | dd(3.6 Hz) | 1H | CH-OH |

The yield of the product obtained was 61%.

The above spectral data and the mode of formation suggested structure of the compound to be N- methyl prolinol.

N- methyl prolinol was then subjected to PCC oxidation by stirring at room temperature in dichloromethane. TLC indicated consumption of the starting compound after 24 hours. After usual workup, we were not able to obtain the corresponding aldehyde. So, we thought of using PDC as oxidizing agent as PCC is slightly acidic in nature and also in literature PDC has been used for synthesis of \( \alpha \)-amino aldehydes from it's corresponding alcohol\(^{84}\). Thus N-methyl prolinol was stirred in dichloromethane with PDC for 24 hours. TLC indicated completion of the reaction as it showed absence of the starting material but, again we were not able to isolate any product. While doing this work, we came across in literature\(^{85}\) another method using IBX as oxidising agent in conjugation with a stable Wittig reagent to obtain the product in one step. Thus, we prepared IBX as per the literature method and treated with N-methyl prolinol along
with 1 eq. of stable phosphorane in DMSO. After stirring for 24 hours, tlc indicated absence of starting compound. Usual workup did not give any product except triphenylphosphine oxide.

Our failure to get N-methyl prolinal or further product prompted us to think of using N-carboethoxy prolinal. We thought of preparing it via N-carboethoxy prolinal (Scheme XXX), wherein proline was to be subjected to treatment with ethylchloroformate to form the N-protected mixed anhydride and subsequent reduction of the mixed anhydride with NaBH₄ in THF would have provided us N-carboethoxy prolinal.

![Scheme XXX](image)

Although, this method is reported to give excellent yields to all commonly used aminoacids, there is no mention of it on L-prolinol. When proline was subjected with the same sequence of reaction, we failed to get the N-carboethoxy prolinal. So, we then subjected N-carboethoxy proline for the mixed anhydride reduction (ethylchloroformate/ sodium borohydride) method but, again we could not get the corresponding N-carboethoxy prolinal. Having failed to get N-carboethoxy prolinal by mixed anhydride method we opted for the more common method of diborane reduction. When we subjected N-carboethoxy proline with NaBH₄-I₂ method, first time we got N-carboethoxy prolinal in 46% yield. When we carried out the same experiment the second time under the same conditions, we got N-methyl prolinal instead. Hence, we thought instead of standardizing this reduction, we can prepare the expected N-carboethoxy prolinal.
product using an alternate approach via prolinol (Scheme XXXI) as we can also use other protecting groups like BOC anhydride.

Thus, proline was reduced with lithium aluminium hydride in THF\textsuperscript{88}. The prolinol obtained was treated with ethylchloroformate in aq. NaOH condition\textsuperscript{89}. The product obtained was characterized by it's spectral properties (given below), which was also identical with the product obtained in the first method of diborane reduction.

\textbf{IR} : $v_{\text{max}}$ 3450, 1750, 1675 cm$^{-1}$

\textbf{PMR} (CDCl$_3$), [Fig.2H]

\begin{tabular}{|c|c|c|c|}
\hline
1.28 & t(6.9 Hz) & 3H & COOCH$_2$CH$_3$ \\
1.79-1.2 & m & 4H & CH$_2$—CH$_2$ \\
3.3-3.4 & m & 1H & CH \\
3.63 & m & 2H & CH$_2$OH \\
4.15 & q(6.9 Hz) & 2H & COOCH$_2$CH$_3$ \\
4.51 & bs & 2H & CH$_2$OH \\
\hline
\end{tabular}

Once N-carboethoxy prolinol was synthesized, we subjected it to one pot IBX method. However, again we failed to get any product.
Fig. 2 H
2.6 CONCLUSION

We have developed a convenient method for the synthesis of 3,5-diarylisoazoles. Studies in total synthesis of ABT-418 are incomplete.
Expt. 2.1 Preparation of 1,3-diphenyl-2-propenone (7a)

Expt. 2.2 Preparation of 1,3-diphenyl-2-propenone-oxime (8a)

Expt. 2.3 Preparation of 3,5-diphenyl isoxazole (9a)
Expt. 2.4 Preparation of 3-[3',4'-methylenedioxyphenyl]-1-phenyl-2-propenone (7b)

Expt. 2.5 Preparation of 3-[3',4'-methylenedioxyphenyl]-1-phenyl-2-propenone oxime (8b)

Expt. 2.6 Preparation of 5-[3',4'-methylendioxyphenyl]3-phenyl isoxazole (9b)
Expt. 2.7  **Preparation of 1-[4'-methoxyphenyl]-3-phenyl-2-propenone (7c)**

\[
\begin{align*}
\text{H}_3\text{CO} & + \text{H}_3\text{C} = \text{CH}_3 \rightarrow \text{H}_3\text{CO} \text{OCH}_3 \\
\text{NaOH} & \quad \text{7c}
\end{align*}
\]

Expt. 2.8  **Preparation of 1-[4'-methoxyphenyl]-3-phenyl-2-propenone oxime (8c)**

\[
\begin{align*}
\text{O} & \quad \text{NH}_2\text{OH} \rightarrow \text{OCH}_3 \\
\text{7c} & \quad \text{8c}
\end{align*}
\]

Expt. 2.9  **Preparation of 3-[4'-methoxyphenyl]-5-phenyl isoxazole (9c)**

\[
\begin{align*}
\text{DDQ, MeOH} & \rightarrow \text{OCH}_3 \\
\text{8c} & \quad \text{9c}
\end{align*}
\]
Expt. 2.10 Preparation of 1,3-bis(4',4'-methoxyphenyl)-2-propenone (7d)

Expt. 2.11 Preparation of 1,3-bis(4',4'-methoxyphenyl)-2-propenone oxime (8d)

Expt. 2.12 Preparation of 3-(4'-methoxyphenyl)-5-(4''-methoxyphenyl) isoxazole (9d)
Expt. 2.13 Preparation of 1-{4'-methoxyphenyl}-3-{3\'',4\''-methyleneedioxyphenyl}-2-propenone (7e)

Expt. 2.14 Preparation of 1-{4'-methoxyphenyl}-3-{3\'',4\''-methyleneedioxyphenyl}-2-propenone oxime (8e)

Expt. 2.15 Preparation of 3-{4'-methoxyphenyl}-5-{3\'',4\''-methyleneedioxyphenyl} isoxazole (9e)
Expt. 2.16 Preparation of 1-phenyl-3-styryl-2-propenone (7f)

Expt. 2.17 Preparation of 1-phenyl-3-styryl-2-propenone oxime (8f)

Expt. 2.18 Preparation of 3-phenyl-5-styryl isoxazole (9f)
**Expt. 2.19 Preparation of Cinnamaldehyde oxime (10)**

![Cinnamaldehyde oxime reaction]

**Expt. 2.20 Preparation of Benzalacetone (11)**

![Benzalacetone reaction]

**Expt. 2.21 Preparation of Benzalacetone oxime (12)**

![Benzalacetone oxime reaction]

**Expt. 2.22 Preparation of β-ionone oxime (13)**

![β-ionone oxime reaction]
Expt. 2.23 Preparation of N-carboethoxy proline (14)

Expt. 2.24 Preparation of N-methyl prolinol (15)

Expt. 2.25 Preparation of L-prolinol (16)

Expt. 2.26 Preparation of N-carboethoxy L-prolinol (17)
Expt.2.1 Preparation of 1,3-diphenyl-2-propenone (7a)

Sodium hydroxide (10%)(1.91g in 17.36 ml water) in ethanol (8.69g, 10.64ml) was kept in ice bath for 10 min. & poured into a mixture of benzaldehyde (4.0g, 30mmol) and acetophenone (4.53g, 30mmol) with constant shaking. Then stirred the reaction mixture for 4 hours at room temperature. Poured the reaction mixture into ice cold water containing dil. HCl. Yellow coloured solid separated, which was recrystallised using ethanol to yield pure yellow crystals (6.12g, 80%) m.p.57°C (lit.68 m.p.57-58°C).

Expt.2.2 Preparation of 1,3-diphenyl-2-propenone oxime (8a)

A mixture of chalcone 7a, (2.0g, 9mmol) hydroxylamine hydrochloride (0.80g, 1mmol), and pyridine (0.87g, 1mmol) in ethanol (10ml) was refluxed on water bath for 45 mins. Ethanol was distilled off and water (10ml) was added. It was then extracted with ether (3 x 10ml). The combined ether layer was washed with dil HCl and water and then dried over anhydrous sodium sulphate. The ether layer was evaporated and the residue obtained was chromatographed over silica gel using ethyl acetate: pet.ether (1:9) as solvent for elution. The initial fractions gave a solid, which was recrystallised using ethanol to yield 8a (1.69g, 79%) m.p.116°C (lit.69 m.p.115-116°C).

Expt.2.3 Preparation of 3,5-diphenyl isoxazole (9a)

Chalcone oxime 8a, (0.5g, 2.4mmol) & DDQ (1.0g, 4.4mmol) was stirred overnight in methanol (5ml) at room temperature. After evaporation of methanol on water bath, the reaction mixture was taken in dichloromethane (20ml) and washed with 2N NaOH (2x15ml). The dichloromethane layer was dried over anhydrous sodium
sulphate, concentrated and adsorbed over silica gel. Column chromatography using ethylacetate:pet.ether (2:8) gave product, which was recrystallised using chloroform:pet.ether (3:7) to give pure white solid (0.37g, 75.33%) m.p.141°C (lit.56 m.p.140-141°C).

**Expt.2.4 Preparation of 3-(3',4'-methylenedioxyphenyl)-1-phenyl-2-propenone (7b)**

Prepared following the same procedure given in expt. 2.1. (2.55, 76%) m.p.120°C (lit.71 m.p.122°C).

**Expt.2.5 Preparation of 3-(3',4'-methylenedioxyphenyl)-1-phenyl-2-propenone oxime (8b)**

Prepared following the same procedure given in expt. 2.2 (1.10g, 52%) m.p.140°C.

**Expt.2.6 Preparation of 5-(3',4'-methylendioxyphenyl)-3-phenyl isoxazole (9b)**

Prepared following the same procedure given in expt. 2.3 (0.14g, 72.27%), m.p.120°C (lit.72 m.p.122-123°C).

**Expt.2.7 Preparation of 1-(4'-methoxyphenyl)-3-phenyl-2-propenone (7c)**

Prepared following the same procedure given in expt. 2.1 (2.6g, 82%) m.p.110°C (lit.73m.p.109-110°C).
Expt. 2.8 Preparation of 1-(4'-methoxyphenyl)-3-phenyl-2-propenone oxime (8c)

Prepared following the same procedure given in expt. 2.2 (0.89g, 42%) m.p.140°C (lit. 74 m.p.140°C).

Expt. 2.9 Preparation of 3-(4'-methoxyphenyl)-5-phenyl isoxazole (9c)

Prepared following the same procedure given in expt. 2.3 (0.140g, 74%) m.p.120°C (lit. 75 m.p.120-121°C).

Expt. 2.10 Preparation of 1,3-bis(4',4'-methoxyphenyl)-2-propenone (7d)

Prepared following the same procedure given in expt. 2.1 (3.15g, 80%) m.p.100°C (lit. 76 m.p.101-102°C).

Expt. 2.11 Preparation of 1,3-bis(4',4'-methoxyphenyl)-2-propenone oxime (8d)

Prepared following the same procedure given in expt 2.2 (0.63g, 30%) m.p.132°C (lit. 74 m.p.132°C).

Expt. 2.12 Preparation of 3-(4'-methoxyphenyl)-5-(4"-methoxyphenyl) isoxazole (9d)

Prepared following the same procedure given in expt. 2.3 (0.12g, 64.2%) m.p.140°C (lit. 77 m.p.141-142°C)
Expt. 2.13 Preparation of 1-(4'-methoxyphenyl)-3-(3'',4''-methylenedioxyphenyl)-2-propenone (7e)

Prepared following the same procedure given in expt. 2.1 (2.82g, 75%) m.p. 130°C (lit. m.p. 131°C).

Expt. 2.14 Preparation of 1-(4'-methoxyphenyl)-3-(3'',4''-methylenedioxyphenyl)-2-propenone oxime (8e)

Prepared following the same procedure given in expt. 2.2 (1.24g, 59%) m.p. 180°C.

Expt. 2.15 Preparation of 3- (4'-methoxyphenyl) -5-(3'',4''-methylenedioxyphenyl) isoxazole (9e)

Prepared following the same procedure given in expt. 2.3 (0.14g, 71%) m.p. 152°C.

Expt. 2.16 Preparation of 1-phenyl-3-styryl-2-propenone (7f)

Prepared following the same procedure given in expt. 2.1 (2.73g, 77%) m.p. 102°C (lit. m.p. 103°C).

Expt. 2.17 Preparation of 1-phenyl-3-styryl-2-propenone oxime (8f)

Prepared following the same procedure given in expt. 2.2 (1.13g, 53.37%) m.p. 135°C (lit. m.p. 135°C).
Expt.2.18 Preparation of 3-phenyl-5-styryl isoxazole (9f)

Prepared following the same procedure given in expt. 2.3 (0.13g, 69.8%) m.p.130°C (lit. m.p.132-134°C).

Expt.2.19 Preparation of Cinnamaldehyde oxime (10)

Cinnamaldehyde (2.0g, 10mmol), hydroxylamine hydrochloride (1.26g, 10mmol), pyridine (0.61g, 1mmol) in ethanol (10ml) was refluxed in water bath for one hour. The solvent was removed on water bath and the residue chromatographed over silica gel using ethylacetate: pet.ether (2:8) afforded oxime 10 (1.31, 59%) m.p.135°C (lit. m.p.134-135°C).

Expt.2.20 Preparation of Benzalacetone (11)

Mixture of sodium hydroxide (10%) (1.91g in 17.36 ml water), benzaldehyde (4.0g, 30mmol) and acetone (4.53g, 30mmol) was stirred at room temperature for two hours. Rendered the mixture acidic to litmus paper. Then, transferred it into a separating funnel and extracted the aqueous layer with ether (2x20ml). The organic extracts were combined and dried over anhydrous sodium sulphate and concentrated to give light yellow solid, which was recrystallised using ethanol (6.12g, 80%) m.p.42°C (lit. m.p.42-43°C).

Expt.2.21 Preparation of Benzalacetone oxime (12)

Compound 11 (2.0g, 10mmol), hydroxylamine hydrochloride (1.26g, 10mmol), pyridine (0.61g, 1mmol) in ethanol (10ml) was refluxed in water bath for one hour. The solvent was removed on water bath and the residue chromatographed over silica gel using
ethylacetate:pet.ether (2:8) afforded oxime 12 (1.31, 59%) m.p.115°C (lit.81 m.p.115-116°C).

Expt.2.22 Preparation of β-ionone oxime (13)

To a stirred solution of β-ionone (1.0g, 5.2mmol), hydroxylamine hydrochloride (0.48g, 6mmol), ethanol (10ml), & water (6ml) was added solid sodium bicarbonate (0.71g). The reaction was refluxed for 90 mins, poured into water (60ml), & extracted with ether (3x20ml) and also with chloroform (2x10ml). The organic extracts were combined and dried over anhydrous sodium sulphate. Evaporation of the solvent gave liquid as product. (1.07, 80%) b.p.76°C (literature82 b.p 75-77°C).

Expt.2.23 Preparation of N-carboethoxy proline (14)

Ethylchloroformate (1.02ml, 1mmol) was added slowly to stirred solution of L-proline (1g, 8mmol) in 1M sodium hydroxide (8.58ml) at 0°C for a period of half an hour in 3 portions. Then, the reaction mixture was allowed to attain room temperature and stirred further for one and a half hour. On completion of the reaction, it was checked for basicity. The mixture was washed with dichloromethane (2x10ml) and was then acidified to pH 1 by adding 6M HCl. The mixture was extracted using dichloromethane (3x15ml). The organic extracts dried over anhydrous sodium sulphate. The solvent was evaporated off under reduced pressure & the product was obtained as low melting white solid (1.5g, 92.24%) m.p.64 (lit.83 m.p.63-64°C).

Expt.2.24 Preparation of N-methyl prolinol (15)

To a stirred solution of lithium aluminium hydride (0.263g, 6.84mmol) in dry ether (10ml) was added N-carboethoxy proline (0.9g, 5.7mmol) in portions over a period of one hour. The stirring was
continued at room temperature for two hours. Water (1ml) was added dropwise to the reaction mixture. The solid separated was filtered off and washed with ether (15ml). The ether layer was further washed with sat. sodium bicarbonate solution (2x10ml). The ether layer was dried over anhydrous sodium sulphate and concentrated on water bath. Evaporation of the solvent gave a liquid (61%).

**Expt.2.25 Preparation of L-prolinol (16)**

To a stirred suspension of lithium aluminium hydride (0.5g, 13.15mmol) was added L-proline (1.0g, 8.6mmol) in dry tetrahydrofuran (22ml) over a period of 40 min. with refluxing and stirring. The reaction mixture was refluxed for six hours. The reaction mixture was cooled and 10% potassium hydroxide (2ml) was slowly added to it, so that the reaction barely refluxes. Then slowly water (1ml) was added to it and the reaction mixture refluxed for further 15 mins. On cooling, the solid mass was filtered, washed with tetrahydrofuran (3x5ml). The organic layer was then dried over anhydrous sodium sulphate & concentrated to give colourless oil (90%).

**Expt.2.26 Preparation of N-carboethoxy L-prolinol (17)**

Ethylchloroformate (1.28g, 10mmol) was added to stirred solution of (16) (1g, 9mmol) in 4N sodium hydroxide solution (6ml) at 0°C, and the mixture was stirred at the same temperature for 30 mins. Then, at room temperature for 30 mins. The reaction mixture was neutralised with 10% hydrochloric acid and extracted with dichloromethane (3x15ml). The extract was dried over anhydrous sodium sulphate and concentrated. The residue was chromatographed using ethylacetate:pet.ether (1:9).
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