CHAPTER 4

A One Pot Tandem Approach for the Synthesis of 5-(Het)aryl Oxazoles from Substituted (Het)aryl Methyl Alcohols and Benzyl Bromides
4.1 Introduction to oxazoles

Oxazole (1,3-Oxazole) is a five membered heterocyclic compound containing an O-atom and N-atom, which is an aromatic, colorless liquid with a boiling point of 69-70 °C and is soluble in water. The oxazole molecule is planar and its structure can be represented by a distorted pentagon. All atoms of oxazole ring are sp²-hybridized orbitals with three nonbonding electron pairs, two on O-atom and another one on N-atom. Since the electronegativity of the N-atom at 3rd position which creates low electron density on C-2 atom. Hence, the electrophilic substitution reaction occur at both 4th or 5th position and the nucleophilic substitution reaction at 2nd position \(^{[1]}\).

![Oxazole Structure](image)

Oxazoles represent an important class of heterocyclic compounds because of their presence in natural products \(^{[2]}\), like macrocyclics and alkaloids \(^{[3,4]}\), and exhibit versatile biological activities \(^{[3,4]}\). In addition, they are also utilized as a scaffold for the construction of many peptides, macrocyclic compounds, and polymers \(^{[2]}\).

4.1.1 Biological significance of oxazoles

Naturally occurring oxazoles were believed to be rare until the end of 1980s, however, now oxazoles form one of the key components of many natural products, particularly derived from marine sources such as, mono-oxazole calyculins, bisoxazole hennoxazoles, and trisoxazole ulapualides \(^{[5-7]}\). They possess significant biological activities including anti-tumor, antibacterial, anti-viral, anti-malarial and immunosuppressive \(^{[5]}\) properties. Some of commercial drugs are having the oxazole moiety are Darglitazone 1, used in the treatment of type II diabetes \(^{[8]}\), and Aleglitazar 2, a peroxisome proliferator-activated receptor agonist for the treatment of type II
Many antibiotics also have an oxazole moiety, such as Pristinamycin IIB, Flopristin, Streptogramin A, Griseovirdin and calcinomycin, display antibiotic activity. Some additional drugs containing oxazole moiety are, Mubritinib, a protein kinase inhibitor for cancer treatment, Muraglitazar 3, used to treat myocardial stroke, infarction or necrosis (heart tissue death), transient ischemic attacks, Ditazole 4, a platelet aggregation inhibitor, Oxaprozin 5, a non-steroidal anti-inflammatory drug used in osteoarthritis and rheumatoid arthritis, Rhizoxin, an antimitotic agent with anti-tumor activity, and Telomestatin which inhibits the telomerase activity of the cancer cells which contains oxazole as an integral moiety in its structure.

Thus, oxazole derivatives have generated considerable attention towards medicinal research, and a large number of investigations on their synthesis and biological significance can be found in the literature. Recently reported oxazole derivatives include: N-aryl-5-aryloxazol-2-amine derivatives as 5-lipoxygenase...
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inhibitors for the treatment of inflammation related diseases including asthma and rheumatoid arthritis \textsuperscript{[21]}, non-steroidal benzo[\textit{d}]oxazole derivatives as anti-inflammatory agents \textsuperscript{[22]}, 5-(4-methoxyphenyl)-oxazole derivatives as an inhibitor for growth and hatch of \textit{Caenorhabditis} elegans (round worm) \textsuperscript{[23]}, anthra[2,3-\textit{d}]oxazole-2-thione-5,10-dione hybrids as antitumor agents and DNA topoisomerase inhibitors \textsuperscript{[24]}, combretastatin conjugated oxazoles as tumor growth inhibitors \textsuperscript{[25]}, 2,4,5-trisubstituted oxazoles as anti-proliferative agents \textsuperscript{[26]}, disubstituted oxazole derivatives exhibited as anti-tuberculotic agents \textsuperscript{[27]}, 2,5-disubstituted oxazole analogues as antibacterial and antifungal agents \textsuperscript{[28]}, aryl substituted 1,3-azoles showed potent activity against mycobacterium tuberculosis \textsuperscript{[27]}, 2,4-disubstituted oxazole benzyl esters as anti-tuberculosis agents \textsuperscript{[29]}, 5-aryl substituted oxazole analogues as HIV-1 inhibitors \textsuperscript{[30]} and bile acid derived oxazoles as fungal growth inhibitors \textsuperscript{[31]}. 

4.1.2 Synthesis of oxazoles in various methods

Owing to their importance, there is a great deal of interest for the development of new strategies for synthesis of oxazoles. Reviews by Turchi and Dewar describe various new as well as old-modified synthetic methodologies for oxazole synthesis \textsuperscript{[32,33]}. The available classical methods for the synthesis of substituted oxazoles are,

(i) Blümlein-Lewy reaction of \( \alpha \)-halo and \( \alpha \)-hydroxy ketones \textbf{6} with acids/amides \textbf{7} via \( O \)-alkylation in refluxing alcoholic media \textsuperscript{[34]} yields oxazoles \textbf{8}.

\begin{align*}
\text{R}_1 \begin{array}{c}
(X) \\
\text{O}
\end{array} + \begin{array}{c}
\text{H}_2\text{N} \\
\text{O}
\end{array} \text{R}_3 & \xrightarrow{\text{MeOH, } \Delta} \begin{array}{c}
\text{R}_2 \\
\text{N}
\end{array} \text{R}_3 \\
\text{R}_1 & \begin{array}{c}
\text{O}
\end{array} \text{H}_2\text{O}, \text{HX} \end{align*}
(ii) R. Robinson’s synthesis of 2-benzyl-5-phenyloxazole 11 from 2,2'-azanediylbis(1-phenylethano-1-one) 9 in presence of concentrated H$_2$SO$_4$ or polyphosphoric acid in 1909 \[^{35}\]. Similarly, 2,5-disubstituted oxazoles were synthesized by S. Gabriel via cyclodehydration of α-acylaminoketones, esters or amides \[^{36,37}\]. Stating material α-acylamino ketones are accessible by Dakin-West reaction \[^{38,39}\].

![Diagram](image1)

(iii) Rhodium, palladium or copper-catalyzed reaction of diazocarbonyl 13 compounds with nitriles 12 afford oxazoles 14 \[^{40-42}\].

![Diagram](image2)

(iv) Copper and ruthenium catalysed cyclization of 3-substituted-1,4,2-dioxazol-5-one 15 with phenylethenes or phenylacetylene 16 afford oxazoles 17 \[^{43}\].

![Diagram](image3)

(v) One-pot p-toluene sulfonic acid (PTSA) catalysed reaction of amides 19 with propargyl alcohols 18 via cyclo-isomerization reaction give oxazoles 20 \[^{44}\].

![Diagram](image4)
(vi) tert-Butyl hydroperoxide (TBHP)-I\(_2\) mediated tandem oxidative cyclization of \(\alpha\)-aminoketones 21 with aldehydes 22\(^{[45]}\), benzyl amines 24 with alkenes 23\(^{[46]}\) afforded oxazole derivatives 25.

\[
\begin{array}{c}
\text{R}_1\text{NH}_2 + \text{H} = \text{O} \xrightarrow{\text{I}_2, \text{TBHP}, \text{NaHCO}_3} \text{O} \xrightarrow{\text{I}_2, \text{TBHP}, \text{DMSO}} \text{R}_1\text{H} + \text{R}_2\text{H} \xrightarrow{\text{H}} \text{R}_2\text{NH}_2
\end{array}
\]

(vii) Silver catalyzed reaction of \(\alpha\)-bromoketones 27 with primary amides 26 obtain oxazole 28 derivatives\(^{[47]}\).

\[
\begin{array}{c}
\text{O} \xrightarrow{\text{AgSbF}_6} \text{R}_1\text{NH}_2 + \text{Br} \xrightarrow{\text{R}_3 = \text{O}} \text{R}_1\text{R}_2\text{R}_3
\end{array}
\]

(viii) An intermolecular cycloaddition of alkynes 29 with nitriles 12, catalysed by gold obtained 2,5-disubstituted oxazoles 30\(^{[48]}\) and the functionalization on oxazole ring were accessed via transition metal catalysed reactions\(^{[49-53]}\).

\[
\begin{array}{c}
\text{R} \equiv \text{H} + \text{R}_1\text{CN} \xrightarrow{\text{Au}, \text{8-Methyl-quinoline}, \text{N-oxide}} \text{R} \xrightarrow{\text{8-Methyl-quinoline}, \text{N-oxide}} \text{R}_1\text{R}_2\text{R}_3
\end{array}
\]

(ix) van Leusen oxazole synthesis, involves the reaction of tosylmethylisocyanide (TosMIC, 32) with aldehydes 31 in the presence of potassium carbonate in methanol \(^{[54]}\). The primary products are 4,5-dihydro-1,3-oxazoles, which are converted into oxazoles 33 by elimination of \(p\)-toluene sulfinic acid.

\[
\begin{array}{c}
\text{O} \xrightarrow{\text{K}_2\text{CO}_3, \text{MeOH}} \text{R}_1\text{R}_2\text{R}_3
\end{array}
\]
However, to synthesize biologically significant 5-(het)aryl oxazoles, TosMIC and aldehydes are widely used as precursors. For instance, modifications of the van Leusen oxazole synthesis involves the reactions of solid phase equivalents of TosMIC with aldehydes [55], quarternary ammonium hydroxide ion-exchange resin catalysed reactions of TosMIC with aldehydes [56], reactions of TosMIC with aldehydes/acid chlorides followed by ultrasound promoted desulfonation [57], reactions of TosMIC with aldehydes in ionic liquid [bmim]Br [58], reactions of aldehydes with benzotrizolylmethylisocyanide, [59] and other methods including Suzuki-Miyaura cross coupling of aryl bromides with oxazoline substituted potassium organotrifluoroborates [60] and asymmetric condensations for oxazolines [61]. Also, few pharmacologically relevant chemotypes have been synthesized through the van Leusen strategy [62]. A literature survey reveals that, aldehyde precursors are most commonly used with TosMIC reagents to access van Leusen oxazoles [32,33].
4.2 Present work

4.2.1 Synthesis of oxazole derivatives

Overall, the synthesis of oxazoles from classical and conventional methods are associated with several disadvantages, such as the need of harsh reaction conditions like high temperatures, toxic metals as catalysts, less stable precursors (aldehydes), and difficulties with syntheses of pre-functionalized intermediates. With this goal, we developed a new approach for the synthesis of 5-aryl oxazoles 35 from TosMIC 32 (Fig. 4.1) with alcohols 34 or benzyl bromides 36 oxidized in propylphosphonic anhydride (T3P®)-DMSO or DMSO media, respectively.

In the beginning of our study, we selected the oxidation of benzyl alcohol 34a to benzaldehyde in T3P®–DMSO and reaction of in situ generated benzaldehyde with TosMIC 32 in the presence of a base as a model reaction (Scheme 4.1). Our initial attempts failed in the presence of bases like triethylamine, Hünig’s base, NaHCO₃, and K₂CO₃. The reason might be that less basic strength and strong alkaline media must be required to neutralize the acidity of tripropyl-diphosphonic acid byproducts from T3P®. Therefore, we have selected aqueous-alcoholic NaOH and KOH as bases in excess. The reaction took place smoothly to give the product 5-phenyloxazole (35a). However, from the point of view of reaction time and yield, aqueous–alcoholic KOH is a suitable base for this reaction (83% yield, Table 4.1, entry 1). In addition, the slight excess of aqueous–alcoholic KOH did not affect the results during the course of the reaction.

![Scheme 4.1](image)

**Scheme 4.1**: Synthesis of 5-(het)aryl oxazoles from (het)aryl methyl alcohols.
With these optimized reaction conditions, we extended the protocol to the synthesis of 5-(p-tolyl)-, 5-(4-tert-butylphenyl)-, 5-(4-methoxy)phenyl-, and 5-(4-nitrophenyl)oxazoles 35(b–e) bearing electron-donating and electron-withdrawing groups from the corresponding substituted aryl methyl alcohols in 68–84% yield (Table 4.1, entries 2–5). Similarly, the methodology is equally extended to benzyl alcohols bearing different halogen atoms, which furnished respective 5-aryl oxazoles 35(f–h) in 70-74% yield (Table 4.1, entries 6–8). Likewise, the protocol is compatible with fused aryl-like 2-naphthylmethyl alcohol, which gives 5-(2-naphthyl)oxazole 35i in 82% yield (Table 4.1, entry 9).

**Table 4.1: Synthesis of 5-(het)aryl oxazoles**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R (34, 35)</th>
<th>35</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>35a</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>4-Me-C\textsubscript{6}H\textsubscript{4}</td>
<td>35b</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>4-tert-Bu-C\textsubscript{6}H\textsubscript{4}</td>
<td>35c</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>4-MeO-C\textsubscript{6}H\textsubscript{4}</td>
<td>35d</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>4-NO\textsubscript{2}-C\textsubscript{6}H\textsubscript{4}</td>
<td>35e</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>4-F-C\textsubscript{6}H\textsubscript{4}</td>
<td>35f</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>4-Cl-C\textsubscript{6}H\textsubscript{4}</td>
<td>35g</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>4-Br-C\textsubscript{6}H\textsubscript{4}</td>
<td>35h</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>2-Naphthyl</td>
<td>35i</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>2-Thienyl</td>
<td>35j</td>
<td>69</td>
</tr>
<tr>
<td>11</td>
<td>2-Furyl</td>
<td>35k</td>
<td>61</td>
</tr>
<tr>
<td>12</td>
<td>Pyridin-2-yl</td>
<td>35l</td>
<td>71</td>
</tr>
<tr>
<td>13</td>
<td>Quinolin-3-yl</td>
<td>35m</td>
<td>75</td>
</tr>
<tr>
<td>14</td>
<td>2-Methoxystyryl</td>
<td>35n</td>
<td>78</td>
</tr>
</tbody>
</table>

This protocol succeeded equally well with 2-thienylmethyl alcohol, furfurol, pyidine-2-yl methyl, and quinolin-3-yl methyl alcohols, which gave the corresponding 5-(het)aryl oxazoles 35(j–m) in 61–75% yields (Table 4.1, entries 10–
Interestingly, allylic alcohol 3-(2-methoxyphenyl)-prop-2-en-1-ol also underwent smooth oxidation and cyclization with TosMIC to give 5-(2-methoxystyryl)oxazole 35n in 78% yield (Table 4.1, entry 14).

**Figure 4.1:** Structure of 5-aryl/alkyl oxazoles 35(a–n).

Further, we have focused our attention to synthesize 5-aryl oxazoles 35(a-i) from different benzyl bromides 36(a-i) via oxidation in DMSO media in the presence of a base (Scheme 4.2). Oxidation of benzyl bromide 36a to benzaldehyde was carried out in the presence of NaHCO₃ and DMSO, followed by cyclization with TosMIC in the presence of various bases like triethylamine, Hünig’s base, NaHCO₃, K₂CO₃, aqueous–alcoholic NaOH and KOH. It was found that KOH is the best base with respect to reaction time and yield of 35a (Table 4.2, entry 1). In a parallel study, this protocol was compared with benzyl chloride instead of benzyl bromide, which results in a longer reaction time and a lower yield.
Scheme 4.2: Synthesis of 5-aryl oxazoles from benzyl bromides.

Thus, with these optimized reaction conditions, we examined the generality of the protocol by carrying the reaction out with \( p \)-tolyl-, 4-\textit{tert}-butylbenzyl-, 4-methoxybenzyl-, and 4-nitrobenzylbromide (Table 4.2, entries 2–5) to furnish the corresponding 5-aryl oxazoles \( 35(b–e) \) in 77–86% yield. Similarly, 4-fluorophenyl-, 4-chlorophenyl-, and 4-bromophenyl oxazoles \( 35(f–h) \) were obtained from the corresponding halogen-substituted benzyl bromides in good yield (Table 4.2, entries 6–8). This method can be equally extended for the synthesis of 5-(2-naphthyl) oxazole (\( 35i \)) from 2-naphthylmethyl bromide in 78% yield (Table 4.2, entry 9).

Table 4.2: Synthesis of 5-aryl oxazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R ) (35, 36)</th>
<th>35</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( C_6H_5 )</td>
<td>( 35a )</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>4-Me-( C_6H_4 )</td>
<td>( 35b )</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>4-\textit{tert}-Bu-( C_6H_4 )</td>
<td>( 35c )</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>4-MeO-( C_6H_4 )</td>
<td>( 35d )</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>4-NO(_2)-( C_6H_4 )</td>
<td>( 35e )</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>4-F-( C_6H_4 )</td>
<td>( 35f )</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>4-Cl-( C_6H_4 )</td>
<td>( 35g )</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>4-Br-( C_6H_4 )</td>
<td>( 35h )</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>2-Naphthyl</td>
<td>( 35i )</td>
<td>78</td>
</tr>
</tbody>
</table>
Notably, 5-(het)aryl oxazoles could not be synthesized due to non-availability of precursors and difficulties in their preparation. The probable mechanism for oxidation of alcohols \[63\] and benzyl bromides \[64\] to aldehydes and van Leusen cyclization \[54\] is given in Scheme 4.3.

**Scheme 4.3:** The plausible mechanism for the synthesis of 5-aryl oxazoles from benzyl alcohols and benzyl bromides.
4.2.2 X-ray diffraction studies of 5-(quinolin-3-yl)oxazole (35m)

The structure of one of the oxazoles, 5-(quinolin-3-yl)oxazole 35m was confirmed by single-crystal X-ray diffraction studies (CCDC reference number 1429231), and its ORTEP diagram is depicted in Fig. 4.2.

Crystal data of compound 5-(quinolin-3-yl)oxazole 35m having molecular formula C₁₂H₈N₂O (M = 196.20 g/mol): N/A, space group C2/c (no.15), a = 12.971(3) Å, b = 17.118(4) Å, c = 8.712(2) Å, β = 96.935(8)°, V = 1920.3(8) Å³, Z = 8, T = 296(2) K, μ(CuKα) = 0.722 mm⁻¹, Dcalc = 1.357 g/cm³, 1935 reflections measured (45.86° ≤ 2Θ ≤ 128.1°), 1192 unique (Rint = 0.0396, Rsigma = N/A) which were used in all calculations. The final R₁ was 0.0667 (>2sigma(I)) and wR₂ was 0.1914 (all data).

Figure 4.2: ORTEP diagram of 5-(quinolin-3-yl)oxazole 35m.
4.3 Experimental section

4.3.1 Materials and methods

As described in Chapter 2 (Section A).

4.3.2 General procedures

(i) Representative procedure for the synthesis 5-(het)aryloxazoles (35a-n) from (het)aryl methyl alcohols

To a solution of (het)aryl methyl alcohol (4.6 mmol) in DMSO (2 mL), T3P® (5.5 mmol, 50% solution in ethyl acetate) was added at 0 °C followed by triethylamine (9.2 mmol) under nitrogen atmosphere. The mixture was stirred at room temperature for 1.5 h. After completion of the reaction (monitored by TLC), KOH (69.0-92.0 mmol) in water-ethanol (1:1::v:v) mixture (3 mL) was added drop wise to the reaction mixture at 0 °C and stirred for 5 min followed by TosMIC (5.0 mmol) addition. The reaction was monitored by TLC followed by evaporation of the ethanol from the reaction mixture under reduced pressure, followed then by dilution with ethyl acetate (2 x 25 mL). The organic layer was washed with water (2 x 20 mL) and brine solution (2 x 20 mL). Then, the organic layer was dried over anhydrous sodium sulphate and concentrated in vacuum to afford crude product. The crude was purified by column chromatography over silica gel (60-120 mesh) using appropriate ratios (8:2) of hexane:ethyl acetate mixture as an eluent.

(ii) Representative procedure for the synthesis 5-(het)aryloxazoles from benzyl bromides (35a-n)

Stirred the mixture of benzyl bromide (2.9 mmol) and NaHCO₃ (4.3 mmol) for 5 min followed by the addition of DMSO (1 mL) at room temperature and reaction was monitored by TLC. Further, drop wise addition of KOH (4.3-5.8 mmol) in water-ethanol (1:1::v:v) mixture (3 mL) at 0 °C and stirred for 5 min followed by the
addition of TosMIC (5.0 mmol), then continued the stirring for 2-3 h. After completion of the reaction (monitored by TLC), evaporated the ethanol from reaction mixture under reduced pressure, followed by dilution with ethyl acetate (2 x 25 mL). The organic layer was washed with water (2 x 20 mL) and brine solution (2 x 20 mL). Then, the organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the crude product. This was then purified by column chromatography over silica gel (60-120 mesh) using appropriate ratios (8:2) of hexane:ethyl acetate mixture as an eluent.

4.3.3 Characterization data

5-Phenyl-oxazole (35a) \(^{[54,59]}\)

Yield 83 %; Pale yellow solid; mp 37-39 °C; FT-IR (cm\(^{-1}\)): 3013, 3006, 2988, 2251, 1661, 1052, 1024, 1005, 658; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.89 (s, 1H, ArH), 7.65-7.62 (m, 2H, ArH), 7.43-7.38 (m, 2H, ArH), 7.34-7.30 (m, 2H, ArH); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 151.5, 150.3, 128.9, 128.6, 127.7, 124.3, 121.4; HRMS: m/z = 145.158 (Calculated), m/z = 146.703 [M+H]\(^+\) (found); Anal. Calcd. for C\(_9\)H\(_7\)N\(_x\)O: C, 74.47; H, 4.86; N, 9.65; O, 11.02; Found: C, 74.48; H, 4.89; N, 9.66.

5-p-Tolyl-oxazole (35b) \(^{[52]}\)

Yield 83 %; White solid; mp 39-41 °C; FT-IR (cm\(^{-1}\)): 3022, 2936, 2383, 1623, 1505, 1484, 1105, 640; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.80 (s, 1H, ArH), 7.46 (dd, \(J_{1,2} = 6.0\) Hz, \(J_{1,1} = 1.6\) Hz, 2H, ArH), 7.21 (s, 1H, ArH), 7.12 (d, \(J = 7.6\) Hz, 2H, ArH), 2.29 (s, 3H, CH\(_3\)); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 151.7, 150.1, 138.6, 129.5, 125.0, 124.3, 120.7, 21.3; HRMS: m/z = 159.185 (Calculated), m/z = 160.088 [M+H]\(^+\) (found); Anal. Calcd. for C\(_{10}\)H\(_9\)NO: C, 75.45; H, 5.70; N, 8.80; O, 10.05; Found: C, 75.47; H, 5.74; N, 8.82.
5-(4-tert-Butyl-phenyl)-oxazole (35c) \[55\]
Yield 80 %; Gummy solid; FT-IR (cm\(^{-1}\)): 3069, 3010, 2985, 2963, 1620, 1565, 1475, 1155, 670; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.87 (s, 1H, Ar\(H\)), 7.58-7.56 (m, 2H), 7.43 (dd, \(J_{1,2} = 6.4\) Hz, \(J_{1,1} = 2.0\) Hz, 2H, Ar\(H\)), 7.29 (s, 1H, Ar\(H\)), 1.33 (s, 9H, t-Bu\(CH_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 151.9, 150.1, 125.8, 125.0, 124.2, 120.9, 120.8, 34.7, 31.1; HRMS: \(m/z = 201.264\) (Calculated), \(m/z = 202.251\) [M+H]\(^+\) (found); Anal. Calcd. for C\(_{13}\)H\(_{15}\)NO: C, 77.58; H, 7.51; N, 6.96; O, 7.95; Found: C, 77.60; H, 7.55; N, 6.98.

5-(4-Methoxy-phenyl)-oxazole (35d) \[59\]
Yield 65 %; Pale Yellow solid; mp 68-70 °C; FT-IR (cm\(^{-1}\)): 3099, 3056, 2991, 1653, 1570, 1489, 1320, 1149, 670; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.87 (s, 1H, Ar\(H\)), 7.58 (dd, \(J_{1,2} = 7.2\) Hz, \(J_{1,1} = 2.4\) Hz, 2H, Ar\(H\)), 7.23 (s, 1H, Ar\(H\)), 6.95 (dd, \(J_{1,2} = 6.4\) Hz, \(J_{1,1} = 2.0\) Hz, 2H, Ar\(H\)), 3.84 (s, 3H, OCH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 159.9, 151.5, 149.9, 125.9, 120.5, 119.8, 114.3, 55.3; HRMS: \(m/z = 201.264\) (Calculated), \(m/z = 202.251\) [M+H]\(^+\) (found). Anal. Calcd. for C\(_{10}\)H\(_9\)NO\(_2\): C, 68.56; H, 5.18; N, 8.00; O, 18.27; Found: C, 68.58; H, 5.21; N, 8.01.

5-(4-Nitro-phenyl)-oxazole (35e) \[52,54\]
Yield 68 %; Yellow solid; mp 137-139 °C; FT-IR (cm\(^{-1}\)): 3112, 3041, 2988, 1666, 1550, 1478, 1360, 1175, 695; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.31-8.26 (m, 3H, Ar\(H\)), 7.84-7.81 (m, 2H, Ar\(H\)), 7.64 (s, 1H, Ar\(H\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 152.3, 151.3, 147.7, 132.5, 125.1, 124.4, 122.6; HRMS: \(m/z = 190.156\) (Calculated), \(m/z = 191.150\) (found).

5-(4-Fluoro-phenyl)-oxazole (35f) \[^{[59]}\]

Yield 74 %; Off white solid; mp 36-38 °C; FT-IR (cm\(^{-1}\)): 3100, 3015, 2963, 2151, 1566, 1425, 1230, 1033, 670; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.88 (s, 1H, ArH), 7.39-7.28 (m, 4H, ArH), 7.01-6.96 (m, 1H, ArH); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 161.8, 150.6, 130.6, 129.6, 122.3, 119.9, 115.5; HRMS: m/z = 163.148 (Calculated), m/z = 164.135 [M+H]^+ (found). Anal. Calcd. for C₉H₆FNO: C, 66.26; H, 3.71; F, 11.64; N, 8.59; O, 9.81; Found: C, 66.28; H, 3.75; N, 8.60.

5-(4-Chloro-phenyl)-oxazole (35g) \[^{[54]}\]

Yield 72 %; Off white solid; mp 65-67 °C; FT-IR (cm\(^{-1}\)): 3112, 3022, 2993, 2187, 1572, 1432, 1265, 1023, 920, 610; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.41 (s, 1H, ArH), 7.60 (dd, \(J_{1,2} = 6.4\) Hz, \(J_{1,1} = 1.6\) Hz, 2H, ArH), 7.52 (s, 1H, ArH), 7.35 (dd, \(J_{1,2} = 6.8\) Hz, \(J_{1,1} = 1.6\) Hz, 2H, ArH); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 152.2, 151.4, 135.9, 129.5, 124.6, 118.4; HRMS: m/z = 179.603 (Calculated), m/z = 180.596 [M+H]^+ (found); Anal. Calcd. for C₉H₆ClNO: C, 60.19; H, 3.37; Cl, 19.74; N, 7.80; O, 8.91; Found: C, 60.21; H, 3.40; N, 7.81.

5-(4-Bromo-phenyl)-oxazole (35h) \[^{[49]}\]

Yield 70 %; Pale yellow solid; mp 77-79 °C; FT-IR (cm\(^{-1}\)): 3101, 3009, 2968, 2165, 1554, 1436, 1245, 1153, 1045, 960, 595; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.96 (s, 1H, ArH), 7.49-7.43 (m, 4H, ArH), 7.32 (s, 1H, ArH); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 152.2, 151.4,
135.9, 129.5, 125.9, 124.6, 118.4; HRMS: m/z = 224.054 (Calculated), m/z = 225.039 [M+H]+ (found). Anal. Calcd. for C₉H₆BrNO: C, 48.25; H, 2.70; Br, 35.66; N, 6.25; O, 7.14; Found: C, 48.27; H, 2.74; N, 6.26.

5-Naphthalen-1-yl-oxazole (35i) \[^{[53]}\]

Yield 82 %; Brown solid; mp 57-59 °C; FT-IR (cm\(^{-1}\)): 3125, 3118, 3059, 2186, 1547, 1432, 1260, 678; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.23 (d, \(J = 9.2\) Hz, 1H, Ar\(H\)), 8.05 (s, 1H, Ar\(H\)), 7.89-7.85 (m, 2H, Ar\(H\)), 7.70 (dd, \(J_{1,2} = 6.8\) Hz, \(J_{1,1} = 1.2\) Hz, 1H, Ar\(H\)), 7.55-7.47 (m, 3H, Ar\(H\)), 7.44 (s, 1H, Ar\(H\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 150.7, 133.8, 130.1, 129.7, 128.7, 127.0, 126.8, 126.6, 126.2, 125.0, 124.9, 124.8; HRMS: m/z = 195.217 (Calculated), m/z = 196.201 [M+H]+ (found); Anal. Calcd. for C\(_{13}\)H\(_9\)NO: C, 79.98; H, 4.65; N, 7.17; O, 8.20; Found: C, 79.99; H, 4.69; N, 7.18.

5-Thiophen-2-yl-oxazole (35j) \[^{[65]}\]

Yield 69 %; Gummy; FT-IR (cm\(^{-1}\)): 3125, 3020, 1631, 1514, 1424, 1216, 772; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.84 (s, 1H, Ar\(H\)), 7.34-7.31 (m, 2H, Ar\(H\)), 7.21 (s, 1H, Ar\(H\)), 7.07 (q, \(J = 3.6\) Hz, 1H, Ar\(H\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 149.8, 147.0, 129.5, 127.7, 125.8, 124.9, 124.8; HRMS: m/z = 151.186 (Calculated), m/z = 152.178 [M+H]+ (found); Anal. Calcd. for C\(_7\)H\(_5\)NOS: C, 55.61; H, 3.33; N, 9.26; O, 10.58; S, 21.21; Found: C, 55.63; H, 3.37; N, 9.28; S, 21.22.

5-Furan-2-yl-oxazole (35k) \[^{[65]}\]

Yield 61 %; Gummy; FT-IR (cm\(^{-1}\)): 3108, 3042, 3004, 2975, 1686, 1561, 1479, 703; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.85 (s, 1H, Ar\(H\)), 7.47 (d, \(J = 2.4\) Hz, 1H, Ar\(H\)), 7.26 (d, \(J = 1.6\) Hz, 1H, Ar\(H\)), 6.65 (d, \(J = 3.2\) Hz, 1H,
ArH), 6.49 (q, J = 2.0 Hz, 1H, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 149.7, 143.9, 143.3, 142.9, 121.4, 111.5, 107.6; HRMS: m/z = 135.120 (Calculated), m/z = 136.109 [M+H]$^+$ (found); Anal. Calcd. for C$_7$H$_5$NO$_2$: C, 62.22; H, 3.73; N, 10.37; O, 23.68; Found: C, 62.24; H, 3.77; N, 10.38.

2-Oxazol-5-yl-pyridine (35l) \[^{65}\]

Yield 71 %; Gummy; FT-IR ($\text{cm}^{-1}$): 3123, 3104, 3012, 2961, 1687, 1576, 1488, 1284, 1208, 1111, 1037, 951, 640; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.61-8.59 (m, 1H, ArH), 7.94 (s, 1H, ArH), 7.72 (td, $J_{1-2}$ = 6.8 Hz, $J_{1-1}$ = 1.6 Hz, 1H, ArH), 7.67 (s, 1H, ArH), 7.63 (dd, $J_{1-2}$ = 7.2 Hz, $J_{1-1}$ = 1.2 Hz, 1H, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 151.2, 151.1, 149.8, 147.0, 136.9, 124.9, 124.7, 123.0; HRMS: m/z = 146.146 (Calculated), m/z = 147.125 [M+H]$^+$ (found); Anal. Calcd. for C$_8$H$_6$N$_2$O: C, 65.75; H, 4.14; N, 19.17; O, 10.95; Found: C, 65.77; H, 4.17; N, 19.18.

5-(quinolin-3-yl)oxazole (35m)

Yield 75 %; Off White solid; mp 100–102 °C; FT-IR ($\text{cm}^{-1}$): 3135, 3067, 2920, 1656, 1537, 1485, 1173, 1004, 940, 763, 647; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.97 (s, 1H, ArH), 8.09 (s, 1H, ArH), 7.93 (d, $J = 8.8$ Hz, 1H, ArH), 7.87 (s, 1H, ArH), 7.62 (d, $J = 8.4$ Hz, 1H, ArH), 7.53 (d, $J = 6.8$ Hz, 1H, ArH), 7.38 (t, $J = 6.4$ Hz, 2H, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 151.0, 148.9, 147.4, 146.4, 130.2, 129.8, 129.2, 127.8, 127.4, 127.3, 122.7, 120.9; HRMS: m/z = 196.205 (Calculated), m/z = 197.213 [M+H]$^+$ (found); Anal. Calcd. for C$_{12}$H$_8$N$_2$O: C, 73.46; H, 4.11; N, 14.28; O, 8.15; Found: C, 73.48; H, 4.15; N, 14.29.
5-[2-(2-Methoxy-phenyl)-vinyl]-oxazole (35n) \(^{166}\)

Yield 78 %; White solid; mp 73-75 °C; FT-IR (cm\(^{-1}\)): 3122, 3044, 2261, 2203, 1925, 1795, 1605, 1564, 1485, 1183, 1098, 1041, 948, 800, 620; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.87 (s, 1H, Ar\(\text{H}\)), 7.53 (dd, \(J_{1-2} = 7.6\) Hz, \(J_{1-1} = 1.6\) Hz, 1H, Ar\(\text{H}\)), 7.44 (d, \(J = 16.4\) Hz, 1H, =CH), 7.33-7.29 (m, 1H, Ar\(\text{H}\)), 7.09-7.94 (m, 4H, =CH and Ar\(\text{H}\)), 3.94 (s, 3H, -OCH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 157.2, 151.0, 150.1, 129.3, 127.1, 125.6, 125.1, 123.6, 120.7, 113.5, 111.0, 55.4; HRMS: \(m/z = 201.221\) (Calculated), \(m/z = 202.211\) [M+H]\(^+\) (found); Anal. Calcd. for C\(_{12}\)H\(_{11}\)NO\(_2\): C, 71.63; H, 5.51; N, 6.96; O, 15.90; Found: C, 71.65; H, 5.55; N, 6.97.

4.4 Conclusion

In summary, developed a new strategy for the synthesis of 5-(het)aryl oxazoles from substituted (het)aryl methyl alcohols and benzyl bromides \textit{via} oxidation in T3P\(^{\circ}\)–DMSO and DMSO media, respectively, followed by the cyclization of \textit{in situ} generated aldehyde with TosMIC in the presence of aqueous–alcoholic KOH with an excellent yield following mild, and eco-friendly protocols. It should be noted that these methods are the substrate-modified green van Leusen oxazole synthesis methods. The noteworthy features of this developed protocol for the tandem reaction are less reaction time, broad functional-group tolerance, and ease of product purification.
4.5 Bibliography


Chapter 4


4.6 Appendices

$^1$H and $^{13}$C NMR spectra of compound 35a
$^1$H and $^{13}$C NMR spectra of compound 35d
$^1$H and $^{13}$C NMR spectra of compound 35g
\(^1\)H and \(^{13}\)C NMR spectra of compound 35k
$^1$H and $^{13}$C NMR spectra of compound 35m
$^1$H and $^{13}$C NMR spectra of compound 35n