Chapter IV

NaIO₄–NaN₃–Mediated Diazidation of Alkenes and Cu(I)-Catalyzed Synthesis of gem-Ditriazoles
Section I:
NaIO₄-NaN₃-mediated diazidation of Alkenes

4.1.1 Introduction

Vicinal diazides are important precursors to 1, 2-diamines,¹ which are useful functional groups present in a variety of natural products, pharmaceutical substances (e.g. D-(+)-biotin),² etc. In addition, 1, 2-diamines find increasing utilization in organic synthesis either as chiral auxiliaries or as metallic ligands especially in the field of catalytic asymmetric synthesis.³ Despite their extensive utility, the development of new method allowing for efficient preparation of 1, 2-diamine remains a stimulating challenge. The general methods of diamine synthesis usually involves the synthesis of vicinal diazides as intermediates via azidation of epoxides⁴ or 1,2 diols⁵ via dimesylation. In contrast, the direct oxidative diazidation of alkenes to diazides presents an attractive and useful strategy.

4.1.2 Review of literature

There are only six methods available in the literature for the direct diazidation of alkenes. Quite recently, few useful methods of introducing vicinal diazide functionality onto alkenes have been reported.⁶ Some of the methods reported in the recent times have been briefly discussed below.

Fristad’s approach (1985)⁷

Fristad et al. have reported the 1, 2-diazidation of some of the alkenes with stoichiometric amounts of Mn(OAc)₂ and NaN₃ to give the corresponding mixture of syn- and anti-diazide products 2 in 51-68% yields. Mechanistically, it was proposed that the alkene is intimately involved in Mn(III)- reduction ligand-transfer oxidation, rather than the intermediacy of free azide radicals. The β-azidoalkyl radical intermediate reacts with a second Mn(III)-N₃ species in a typical ligand-transfer fashion to complete the double addition. The yield of 1, 2-diazone was highly
dependent on the reactant concentrations. The major side product in the reaction was the 1-azidoalkane. Higher reactant concentrations, however, allowed good selectivity for the 1, 2-diazidoalkanes over 1-azidoalkanes (Scheme 1).

\[
\text{Scheme 1: (i) Mn(OAc)}_2 (4.80 \text{ mmol), NaN}_3 (72 \text{ mmol), AcOH (25 mL), 85-110 ^\circ \text{C, 10-30 min, 51-68%}}.
\]

Moriarty’s approach (1986)\(^8\)

Moriarty \textit{et al.} have reported 1, 2-diazidation of a variety of alkenes such as 3 with PhIO-AcOH-NaN\(_3\) reagent system to give vicinal diazides 4 in 34-85% yields, along with \(\alpha\)-azidoketone 5 in 14% yields. This approach involves initial electrophilic attack of the hypervalent iodine (PhIO) species upon the C=C double bond to yield cationic intermediate, which is attacked by azide anion. Subsequent reductive elimination of iodobenzene with attack by a second azide anion produced the vicinal diazides. This pathway accounts for the lack of stereoselectivity (Scheme 2).

\[
\text{Scheme 2: (i) PhIO (0.01 mol), NaN}_3 (0.04 \text{ mol), AcOH (25 mL), 50 ^\circ \text{C, 3 h, 34-85%}}.
\]

Arimoto’s approach (1989)\(^9\)

In this approach, \(\beta\)-substituted allyltrimethylsilane 6 were converted into the corresponding \textit{vic}-diazides 7 with (PhIO) and TMSN\(_3\) in moderate yields (Scheme 3).
Snider’s approach (1998)\textsuperscript{10}

Snider \textit{et al.} have described that alkenes and glycals react with Mn(OAc)\textsubscript{3}.2H\textsubscript{2}O and NaN\textsubscript{3} in 9:1 acetonitrile/trifluoroacetic acid to give 1, 2-diazides in >80\% yields. Glycals could not undergo \textit{vic}-diazidation under Fristad’s condition. The salient feature of this method is that, the 1, 2-diazidation of glycols \textsuperscript{8} has been achieved simply by changing AcOH used in Fristad’s method by CF\textsubscript{3}CO\textsubscript{2}H at (-20°C) and the reaction proceeding within comparatively less reaction time (3 min). The extensive synthetic utility of glycopyranosyl azides (9 \& 10) for the preparation of glycosylated asparagine derivatives,\textsuperscript{11} renders this method more attractive (\textbf{Scheme 4}).

\begin{equation}
\begin{array}{c}
\text{Scheme 3: (i) (PhIO)n, TMSN}_3, \text{CH}_2\text{Cl}_2, \\
-78 - 25 \text{ °C, 52-86\%}.
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{Snider’s approach (1998)}\textsuperscript{10}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{Austin’s approach (2004)}\textsuperscript{12}
\end{array}
\end{equation}

Austin \textit{et al.} have studied the diazidation of pyrazinone 11 to give the corresponding syn- and anti-diazidopyrazinone 12 in up to 62\% yield. The bimolecular nucleophilic substitution by excess azide, under the solution-phase conditions, resulted in syn-diazide 13 product, whereas the second azide displacement reaction was expected to
proceed through addition from the less sterically hindered face, under solid-phase conditions, to produce the anti-diazide product 12. syn-Diazidopyrazinone 13 was used as an intermediate in the total synthesis of (±)-dibromophakellstatin. Another interesting feature is that, this methodology has been extensively applied in the syn azidation of various additional alkene substrates and their use in the synthesis of guanidine-containing natural products (Scheme 5).

Scheme 5: (i) ICl (5.09 mmol), NaN₃ (17.4 mmol), MeCN (6 ml), -10 °C, 3 h; (ii) PhI(OAc)₂ (4.38 mmol), TMSN₃ (9.04 mmol), -10 °C, 10 h.

Ohba’s approach (2005)₁³

In this approach, the authors have described direct a vic-diazidation of α-pinene 14 to give the corresponding mixtures of diazides 15 and 16 by using Mn(OAc)₂ and NaN₃ in acetic acid. This was the first example of conversion of α-pinene to 2,3-pinane diazide. The absolute configuration of anti- and syn-pinane diazides were determined by 2D ¹HNMR and X-ray crystallography. Easy availability of α-pinene as an enantiomeric pure sample and ease of chemical modification rendered this method more practical (Scheme 6).
Pfaendler’s approach (2004)\textsuperscript{14}

Pfaendler \textit{et al.} have reported a mild and two-step sequence for the \textit{vic}-diazidation of olefins that produced diazides 19 in 78\% yields. The sequence included azidoiodination of alkenes 17 followed by substitution with azide ion to give 1,2-diazido product 19. The use of DMSO as solvent rather than DMF enhanced the reaction rate, and reduced the temperature from 100 °C to 25 °C. (\textbf{Scheme 7}).

\begin{center}
\begin{tikzpicture}
    \node (a) at (0,0) {17}
    \node (b) at (2,0) {BnO}\node (c) at (4,0) {\textbf{i}}
    \node (d) at (6,0) {18}
    \node (e) at (0,-2) {19}
    \node (f) at (2,-2) {BnO}\node (g) at (4,-2) {\textbf{ii}}
    \node (h) at (6,-2) {N_3} \node (i) at (7,-2) {N_3} \node (j) at (8,-2) {N_3}

    \node (k) at (0,0.5) {i: ICl (1.30 mmol), NaN\textsubscript{3} (3.25 mmol), CH\textsubscript{3}CN (1 mL) 2.5 h, 99\%; ii) NaN\textsubscript{3} (1.5 mmol), DMSO (1 mL), 20 h, 78\%}

\end{tikzpicture}
\end{center}

\textbf{Scheme 7:} (i) ICl (1.30 mmol), NaN\textsubscript{3} (3.25 mmol), CH\textsubscript{3}CN (1 mL) 2.5 h, 99\%; ii) NaN\textsubscript{3} (1.5 mmol), DMSO (1 mL), 20 h, 78\%.

\subsection*{4.1.3 Present Work}

\subsection*{4.1.3.1 Objective}

In recent years, as can be seen from the above discussions, a considerable progress has been made in diazidation of various types of alkenes. It has become a major tool of synthetic organic chemistry, thus providing an efficient and versatile access to new diazido compounds. The reported methods include combinations like Mn\textsuperscript{3+}-NaN\textsubscript{3} (large excess)- AcOH\textsuperscript{7} or TFA\textsuperscript{10}, Fe\textsuperscript{2+}-H\textsubscript{2}O\textsubscript{2}-NaN\textsubscript{3}\textsuperscript{15}, PhIO-NaN\textsubscript{3}-AcOH\textsuperscript{8} and S\textsubscript{N}2 displacements involving multi-steps.\textsuperscript{14} However, some of them suffer from certain drawbacks like low yields, multi-step reaction sequences, expensive metal salts and oxidants. In this context, a more practical and efficient synthesis of 1,2-diazidoalkanes is highly desirable. Moreover, combination such as NaIO\textsubscript{4}-NaN\textsubscript{3}-AcOH has not been reported for the diazidation of alkenes. In this section we describe a new NaIO\textsubscript{4}-
NaN₃-AcOH- mediated procedure for the direct diazidation of various aromatic as well as aliphatic alkenes that affords the corresponding vicinal diazides (2) in excellent yields (Table 1).

4.1.3.2 Results and Discussion

During the course of this study of NaIO₄-mediated oxidative functionalization of alkenes, we observed that the treatment of alkenes 20a-j with stoichiometric amounts of NaIO₄ and sodium azide in DMSO:AcOH (4:1) as solvent at 75 °C, produced diazides 21a-j in good yields. In particular, when styrene 20a was subjected to oxidative functionalization with NaIO₄ (1 equiv) in the presence of NaN₃ (3 equiv) in DMSO:AcOH (4:1) as solvent at 75 °C, gave diazide 21a in 75% yield (Scheme 8).

![Scheme 8](image)

To study the generality of the reaction, a variety of alkenes were subjected to diazidation with NaIO₄-NaN₃ reagent combination, and the results are presented in (Table 1). Aromatic olefins as well as aliphatic olefins gave good yields of the corresponding 1,2-diazides. Internal olefins such as indene and cyclooctene have proceeded to give products in excellent yields with 1:1 diastereoselectivity (20g and 20i) as confirmed by their ¹H NMR spectra. However, no reaction took place in the case of α, β–unsaturated carbonyl compounds, which may be a limitation of this method.
Table 1: NaIO₄-mediated diazidation of alkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (20a-j)</th>
<th>Products (21a-j)</th>
<th>Yield (%)</th>
<th>anti : syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>styrene</td>
<td><img src="image" alt="styrene" /></td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td>b</td>
<td>4-fluorostyrene</td>
<td><img src="image" alt="4-fluorostyrene" /></td>
<td>89</td>
<td>-</td>
</tr>
<tr>
<td>c</td>
<td>2-chlorostyrene</td>
<td><img src="image" alt="2-chlorostyrene" /></td>
<td>85</td>
<td>-</td>
</tr>
<tr>
<td>d</td>
<td>4-bromostyrene</td>
<td><img src="image" alt="4-bromostyrene" /></td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>e</td>
<td>3-methoxystyrene</td>
<td><img src="image" alt="3-methoxystyrene" /></td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>f</td>
<td>methylenedioxyvinylbenzene</td>
<td><img src="image" alt="methylenedioxyvinylbenzene" /></td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>g</td>
<td>indene</td>
<td><img src="image" alt="indene" /></td>
<td>75</td>
<td>1:1</td>
</tr>
<tr>
<td>h</td>
<td>vinylcyclohexane</td>
<td><img src="image" alt="vinylcyclohexane" /></td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td>i</td>
<td>cyclooctene</td>
<td><img src="image" alt="cyclooctene" /></td>
<td>60</td>
<td>1:1</td>
</tr>
</tbody>
</table>
Reaction conditions: \(^a\)alkenes (5 mmol), \(\text{NaIO}_4\) (5 mmol), \(\text{NaN}_3\) (15 mmol), 20ml DMSO: AcOH (4:1), 75 °C, 2 h; \(^b\) yields refer to isolated yield after column chromatography.

The formation of diazides \(21a-j\) was confirmed by \(^1\)H and \(^{13}\)C NMR and IR spectroscopy.

Fig. 1: \(^1\)H and \(^{13}\)C NMR of styrene diazide \(21a\)
Example 1: The $^1$H NMR spectrum of 21a showed a doublet of doublet at $\delta$ 4.65 (1H) for benzylic proton and a typical multiplet at $\delta$ 3.37-3.55 (m, 2H) for homobenzylic protons. Its $^{13}$C NMR spectrum displayed typical signals at $\delta$ 65.4 and 55.8 for the benzylic and homobenzylic carbons respectively (Fig. 1). Its IR spectrum displayed a strong absorption band at 2103 cm$^{-1}$ confirming the formation of azide function. The diastereomeric ratios (anti: syn) for internal olefins were determined from $^1$H NMR spectroscopic studies (dr = 1:1).

Fig. 2: $^1$H and $^{13}$C NMR of styrene diazide 21h
Example 2: The $^1$H NMR spectrum of 21h showed a multiplets at $\delta$ 3.25-3.47 (3H) for protons attached to azidocarbons (N$_3$CH$_2$ & N$_3$CH) and multiplets in the range $\delta$ 1.08-1.79 for cyclohexane ring protons. The disappearance of signals in the olefinic region substantiated the formation of diazide 21h. Its $^{13}$C NMR spectrum displayed typical two signals at $\delta$ 67.5 and 52.9 for the azidocarbons (N$_3$CH$_2$ & N$_3$CH) respectively (Fig. 2).

4.1.4 Mechanism

The probable mechanism for the direct diazidation of alkenes to the corresponding diazides is proposed, that involves a radical pathway. Accordingly, the NaIO$_4$ is able to oxidize NaN$_3$ to give the corresponding azide radical,$^{16}$ which is then added onto alkene to give the secondary radical 23. Subsequently, the secondary radical is further believed to be trapped with another azide radical to give diazides (Scheme 9).

![Scheme 9: Proposed mechanism for the 1,2-diazidation of alkenes](image)

4.1.5. Conclusion

In conclusion, we have developed a new reagent system consisting of NaIO$_4$-NaN$_3$ as a new efficient system suitable for direct diazidation of alkenes into their corresponding vicinal diazides. The procedure is simple and high yielding. The reaction is believed to proceed \textit{via} radical pathway.
4.1.6. Experimental

General experimental procedure for 1,2-diazidation of alkenes:

To a suspension of NaN\(_3\) (0.975 g, 15 mmol) and NaIO\(_4\) (1.069 g, 5 mmol) in 20 mL of DMSO: glacial AcOH (4: 1) was added alkenes 20a-j (5 mmol) and the reaction mixture was stirred at 75 °C for 2 h until the mixture became dark brown in color. After the reaction was complete (monitored by TLC) it was poured into water (100 ml) and extracted with EtOAc (3 × 50 ml). The combined organic layers were washed with a saturated solution of NaHCO\(_3\) (50 ml) followed by aqueous Na\(_2\)S\(_2\)O\(_3\) (5%, 50 ml), dried over anhyd. Na\(_2\)SO\(_4\). Distillation of the organic layer under reduced pressure gave the crude diazides, which was subjected to column purification using hexane/ethyl acetate (19:1) as eluent to obtain pure 1,2-diazides 21a-j.

1,2-Diazido-1-phenylethane (21a)

Yield: 75%; pale yellow liquid; IR (neat, cm\(^{-1}\)): \(\nu_{\text{max}}\) 700, 759, 1257, 1454, 2100, 2926; \(^1\text{H-NMR}\) (200 MHz, CDCl\(_3\)): \(\delta\) 3.37-3.55 (m, 2H), 4.65 (dd, \(J = 5.4, 7.8\) Hz, 1H), 7.29-7.55 (m, 5H); \(^{13}\text{C-NMR}\) (50 MHz, CDCl\(_3\)): \(\delta\) 55.8, 65.4, 126.8, 128.9, 129.0, 136.3; Anal. Calcd for C\(_8\)H\(_8\)N\(_6\): C, 51.06; H, 4.28; N, 44.66; Found: C, 51.30; H, 4.08; N, 44.50%.

1-Fluoro-4-(1,2-diazidoethyl) benzene (21b)

Yield: 89%; pale yellow liquid; IR (neat, cm\(^{-1}\)): \(\nu_{\text{max}}\) 1254, 2103, 2940; \(^1\text{H NMR}\) (200 MHz, CDCl\(_3\)): \(\delta\) 3.44 (dd, \(J = 7.7, 12.7\) Hz, 2H), 4.65 (dd, \(J = 5.6, 7.7\) Hz, 1H), 7.10 (m, 2H), 7.32 (m, 2H); \(^{13}\text{C NMR}\) (50 MHz, CDCl\(_3\)): \(\delta\) 55.9, 64.8, 115.9, 116.3, 128.7, 128.8, 32.2, 132.3, 160.4, 165.4; Anal. Calcd for C\(_8\)H\(_7\)FN\(_6\): C, 46.60; H, 4.28; N, 40.70; Found: C, 46.60; H, 3.42; N, 40.76%.

1-Chloro-2-(1,2-diazidoethyl)benzene (21c)

Yield: 85%; pale yellow liquid; IR (neat, cm\(^{-1}\)): \(\nu_{\text{max}}\) 665, 756, 1037, 1255, 1336, 1437,
Diazidation

1474, 2100, 2936, 3063; $^1$HNMR (200 MHz, CDCl$_3$): $\delta$ 3.40 (dd, $J = 4.04, 12.58$ Hz, 1H), 3.53 (dd, $J = 8.1, 12.8$ Hz, 1H), 5.22 (dd, $J = 3.81, 8.54$ Hz, 1H), 7.32 (m, 2H); 7.40 (m, 1H), 7.47 (m, 1H); $^{13}$CNMR (50 MHz, CDCl$_3$): $\delta$ 54.8, 62.1, 127.5, 128.1, 129.9, 132.6, 134.1; Anal. Calcd for C$_8$H$_7$ClN$_6$: C, 43.16; H, 3.17; N, 37.75; Found: C, 43.15; H, 3.17; N, 37.76%.

1-Bromo-4-(1,2-diazidoethyl)benzene (21d)

Yield: 90%; pale yellow liquid; IR (neat, cm$^{-1}$): $\nu_{\text{max}}$ 719, 856, 1073, 1267, 1489, 1590, 2076, 2929; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.44 (dd, $J = 7.75, 12.68$ Hz, 2H), 4.62 (dd, $J = 5.36, 7.62$ Hz, 2H), 7.24 (m, 2H), 7.55 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 56, 94.2, 157.4, 158.9; Anal. Calcd for C$_8$H$_7$BrN$_6$: C, 35.98; H, 2.64; N, 31.47; Found: C, 35.96; H, 2.64; N, 31.48%.

1-(1,2-Diazidoethyl)-3-methoxybenzene (21e)

Yield: 90%; pale yellow liquid; IR (neat, cm$^{-1}$): $\nu_{\text{max}}$ 783, 1153, 1267, 1437, 1601, 2099, 2937; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.45 (dd, $J = 7.9, 12.7$ Hz, 2H), 3.83 (s, 3H), 4.64 (dd, $J = 5.5, 7.9$ Hz, 1H), 6.88 (m, 3H), 7.32 (m, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 55.1, 55.8, 65.3, 112.5, 114.2, 118.9, 130, 137.7, 159.9; Anal. Calcd for C$_9$H$_{10}$N$_6$O: C, 49.54; H, 4.62; N, 38.51; Found: C, 49.55; H, 4.61; N, 38.51%.

5-(1, 2-Diazidoethyl)benzo[1,3]dioxole (21f)

Yield: 90%; pale yellow viscous liquid; IR (neat, cm$^{-1}$): $\nu_{\text{max}}$ 730, 933, 1102, 1247, 1444, 1504, 2100, 2902; $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 3.40 (dd, $J = 8.09, 12.81$ Hz, 2H), 4.56 (dd, $J = 5.39, 7.79$ Hz, 1H), 6.00 (s, 2H), 6.80 (m, 3H), 7.32 (m, 1H); $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ 55.9, 65.3, 101.4, 107, 108.5, 120.8, 130.1, 148.3; Anal. Calcd for C$_9$H$_8$N$_6$O$_2$: C, 46.55; H, 3.47; N, 36.19; Found: C, 46.53; H, 3.47; N, 36.20%.

1, 2-Diazidoindane (21g)

Yield: 70%; pale yellow viscous liquid; mixture of anti : syn (1:1); IR (neat, cm$^{-1}$): $\nu_{\text{max}}$
704, 738, 1265, 2104, 2926; \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \(\delta\) 2.94 (dd, \(J = 6.7, 16\) Hz, 1H), 3.17 (d, \(J = 6.7\) Hz, 2H), 3.35 (dd, \(J = 6.8, 16\) Hz, 1H), 4.16 (dd, \(J = 6.7, 12\) Hz, 1H), 4.29 (dd, \(J = 6.7, 12\) Hz, 1H), 4.76 (d, \(J = 5.6\) Hz, 1H), 4.82 (d, \(J = 5.7\) Hz, 1H), 7.23-7.42 (m, 8H); \textsuperscript{13}C NMR (50 MHz, CDCl\textsubscript{3}): \(\delta\) 35.4, 35.9, 63.9, 66.8, 67.5, 124.41, 124.7, 125.0, 125.2, 127.5, 127.6, 129.3, 129.5, 137.4, 137.6, 138.9, 139.6; \textsuperset{Anal.} Calcd for C\textsubscript{10}H\textsubscript{10}N\textsubscript{6}: C, 56.07; H, 4.71; N, 39.23; Found: C, 55.60; H, 4.88; N, 39.50%.

1, 2-Diazido-1-cyclohexylethane (21h)

\textbf{Yield:} 80%; pale yellow liquid; \textbf{IR} (neat, cm\textsuperscript{-1}): \(\nu_{\text{max}}\) 1252, 2102, 2937; \textsuperscript{1}H-NMR (200 MHz, CDCl\textsubscript{3}): \(\delta\) 0.96-1.35 (m, 5H), 1.45-1.17 (m, 6H), 3.21-3.30 (m, 1H), 3.36-3.49 (m, 2H); \textsuperscript{13}C-NMR (50 MHz, CDCl\textsubscript{3}): \(\delta\) 25.7, 25.8, 28.5, 29.6, 40.0, 52.9, 67.5; \textsuperset{Anal} Calcd for C\textsubscript{8}H\textsubscript{14}N\textsubscript{6}: C, 49.47; H, 7.26; N, 43.27; Found: C, 49.25; H, 7.50; N, 43.20%.

1, 2-Diazidocyclooctane (21i)

\textbf{Yield:} 60%; pale yellow viscous liquid; \textbf{IR} (neat, cm\textsuperscript{-1}): \(\nu_{\text{max}}\) 1252, 2094; \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \(\delta\) 1.56 (m, 6H), 1.81 (m, 6H), 3.55 (m, 1H), 3.73 (m, 1H); \textsuperscript{13}C NMR (50 MHz, CDCl\textsubscript{3}): \(\delta\) 23.50, 26.5, 27.0, 27.3, 28.1, 29.3 61.5, 63.3; \textsuperset{Anal} Calcd for C\textsubscript{8}H\textsubscript{14}N\textsubscript{6}: C, 49.47; H, 7.26; N, 43.27; Found: C, 49.45; H, 7.28; N, 43.29%.

1, 2-Diazidohexane (21j)

\textbf{Yield:} 70%; pale yellow viscous liquid; \textbf{IR} (neat, cm\textsuperscript{-1}): \(\nu_{\text{max}}\) 1253, 2103, 2930; \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \(\delta\) 0.93 (t, \(J = 6.7\) Hz, 3H), 1.25-1.41 (m, 4H), 1.51-1.58 (m, 2H), 3.25-3.53 (m, 3H); \textsuperscript{13}CNMR (50 MHz, CDCl\textsubscript{3}): \(\delta\) 13.7, 22.2, 27.8, 31.3, 54.7, 61.9; \textsuperset{Anal.} Calcd for C\textsubscript{6}H\textsubscript{12}N\textsubscript{6}: C, 42.84; H, 7.19; N, 49.96; Found: C, 42.50; H, 7.31; N, 49.90%.
SECTION II:
Synthesis of gem-Ditriazoles from α,α-Diazido Ketones

4.2.1 Introduction and Pharmacology

Triazoles, like many other five membered heterocyclic compounds are used very often in the pharmacological and medicinal applications. 1,2,3–Triazole and its derivatives enhanced considerable attention for the past few decades due to their chemotherapeutical value. Many 1,2,3–triazole derivatives are found to be more potent anti-microbial,\textsuperscript{18} anti-inflammatory,\textsuperscript{19} analgesic,\textsuperscript{20} local anesthetic,\textsuperscript{21} anti-allergic, anti-convulsant,\textsuperscript{22} anti-neoplastic,\textsuperscript{23} anti-malarial,\textsuperscript{24} anti-HIV\textsuperscript{25} and anti-cancer activities.\textsuperscript{26} Some of the 1,2,3-triazoles are also used as deoxyribose nucleic acid (DNA) cleaving agents\textsuperscript{27} and potassium channel activators.\textsuperscript{28} These moieties have been widely used in the synthetic intermediates and industrial applications, such as dyes, anti corrosive agents, photo stabilizers, photographic materials and agrochemicals.\textsuperscript{29} Thus, 1,2,3-triazoles are useful building blocks in chemistry and are stable to moisture, oxygen, light and also metabolism in the body. Moreover, these moieties can be turned to form powerful pharmacophores and also play an important role in bio-conjugation. 1,2,3-Triazole moieties are attractive connecting units, since they are stable to metabolic degradation and capable of hydrogen bonding which can be favorable in binding of biomolecular targets.

4.2.2 Review of Literature

Literature search reveals that there are no reports available for the syntheses of gem-ditriazoles.

4.2.3 Present Work

4.2.3.1 Objective

One of the most attractive ways to prepare these compounds involve the thermal 1,3-dipolar cycloaddition of azides with alkynes, pioneered by Huisgen.\textsuperscript{17} This section
deals with the synthesis of some novel gem-ditriazoles from several α,α-diazidoketones, prepared from the respective aromatic ketones via NaIO₄–NaN₃ mediated α,α-diazidation, in view of pharmacological significance of triazole derivatives.

4.2.3.2 Results and Discussion

During the course of this study of NaIO₄-mediated oxidative α,α-diazidation of arylketones, we found that treatment of α,α-diazidoketones 26a-f with phenylacetylene (2 equiv) in the presence of Cu(I) as the catalyst in toluene at 80 °C, provided gem-α,α-ditriazole aryl ketones 27a-f in high yields (85-88%) (Scheme 11). The starting material i.e. α, α-diazidoketones 26a-f were prepared by the NaIO₄-NaN₃ mediated diazidation of corresponding aromatic ketones 25a-f in excellent yields (Scheme 10).³⁰

![Scheme 10](image)

**Scheme 10:** (i) ketone (5 mmol), NaIO₄ (5 mmol), NaN₃ (15 mmol), DMSO:AcOH (4:1), 75 °C, 4 h.

In particular when 2,2-diazido-1-phenylpropan-1-one 26a was subjected to 1,3-cycloaddition reaction with phenylacetylene (2 equiv) in the presence Cu(I) as the catalyst gave diatriazole 27a in 88% yield. Range of substrates have been screened including open chain as well as cyclic aromatic ketones. The sterically hindered diazidoketones like 26c and 26d also were converted in to α,α-geminal ditriazole 27c and 27d in very good yield 85% each. Continuation of reaction more than 8 h did not improve the yields (Table 2).
Scheme 11: (i) Cul (5 mol%), toluene, 80 °C, 8 h.

Table 2: Cul-mediated synthesis of gem-α,α-ditriazole aryl ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (26a-f)</th>
<th>Products (27a-f)</th>
<th>Yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td><img src="image1" alt="Substrate 26a" /></td>
<td><img src="image2" alt="Product 27a" /></td>
<td>88</td>
</tr>
<tr>
<td>b</td>
<td><img src="image3" alt="Substrate 26b" /></td>
<td><img src="image4" alt="Product 27b" /></td>
<td>87</td>
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<tr>
<td>c</td>
<td><img src="image5" alt="Substrate 26c" /></td>
<td><img src="image6" alt="Product 27c" /></td>
<td>85</td>
</tr>
<tr>
<td>d</td>
<td><img src="image7" alt="Substrate 26d" /></td>
<td><img src="image8" alt="Product 27d" /></td>
<td>85</td>
</tr>
<tr>
<td>e</td>
<td><img src="image9" alt="Substrate 26e" /></td>
<td><img src="image10" alt="Product 27e" /></td>
<td>87</td>
</tr>
</tbody>
</table>
Reaction conditions: α,α-diazidoketones (5 mmol), phenyl acetylene (10 mmol), CuI (0.25 mmol), 20 ml, toluene 80 °C, 8 h; yields refer to isolated yield after column chromatography.

The formation of gem-α,α-ditriazole 27a-f was confirmed by $^1$H and $^{13}$C NMR and IR spectroscopy.

**Example 1:** The $^1$H NMR spectrum of 27a showed a typical singlet at $\delta$ 8.13 for alkene protons in the triazole ring and multiplets at $\delta$ 7.30-7.45 and 7.82-7.86 for aromatic protons. Its $^{13}$C NMR spectrum showed two typical signals at $\delta$ 148.5 and 191.8 for the alkenic carbon in the triazole ring and carbonyl carbon respectively. The disappearance of signal at 2108 cm$^{-1}$ in its IR spectrum further substantiated the formation of triazole ring (**Fig. 3**).
Example 2: The $^1$H NMR spectra showed a typical signals at $\delta$ 2.68-2.91 and 3.31-3.50 for the four aliphatic protons of 27c whereas typical singlets at $\delta$ 7.66 and 7.33 for alkenic protons in the triazole ring and multiplets at $\delta$ 6.78-7.42 and 7.78-7.81 for aromatic protons.
Fig. 4: $^1$H, $^{13}$C NMR and LCMS spectra of ditriazole 27c

Its $^{13}$C NMR spectrum displayed two typical signals at $\delta$ 24.8 and 32.0 for the $\beta$- and $\alpha$-aliphatic carbons respectively. The signals at $\delta$ 148 and 191.8 for the quaternary carbons in the triazole ring and carbonyl carbon respectively. Its LCMS chromatogram showed the molecular ion peak at m/z for [M + Na]$^+$, 455.12 (Fig. 4).

4.2.4. Conclusion

In conclusion, we have provided an efficient method for the synthesis of gem-$\alpha,\alpha$-ditriazole aryl ketones via the CuI catalyzed 1,3-dipolar cycloaddition reaction.
between \(\alpha,\alpha\)-diazidoketones and phenylacetylene. The compounds are believed to be important owing to the various significant properties of triazoles. The procedure is simple and high yielding.

4.2.5. Experimental

**General experimental procedure for the synthesis of gem-ditriazoles from \(\alpha,\alpha\)-diazido ketones:**

To a suspension of Cul (0.25 mmol) and phenyl acetylene (10 mmol) in 20 mL of toluene was added \(\alpha,\alpha\)-diazidoketones 26a-f (5 mmol), as the case may be, and the reaction mixture was stirred at 80 °C for 8 h. It was monitored by TLC and then the reaction mixture was poured into water (100 ml) and extracted with EtOAc (3 \(\times\) 20 ml). The combined organic layers were washed with a saturated solution of aqueous Na\(_2\)S\(_2\)O\(_3\) (5%, 50 ml), dried over anhyd. Na\(_2\)SO\(_4\). Concentration of the organic layer under reduced pressure gave crude ditriazoles, which was subjected to column purification using hexane/ethyl acetate (9:1) as eluent to obtain pure \(\text{gem-}\alpha,\alpha\)-ditriazole aryl ketones 27a-f.

**1-Phenyl-2,2-bis(4-phenyl-1H-1,2,3-triazol-1-yl)propan-1-one (27a)**

**Yield:** 88%; pale yellow solid; **mp:** 195-200 °C; **IR** (neat, cm\(^{-1}\)): \(\nu_{\text{max}}\) 691, 764, 1070, 1452, 1697, 1741, 2921; **\(^1\)H NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 2.99 (s, 3H), 7.42 (m, 11H), 7.82 (dd, \(J = 7.6\) and 12.2 Hz, 4H), 8.13 (s, 2H); **\(^13\)C NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 23.2, 81.8, 119.2, 126, 128.7, 129, 129.4, 129.6, 132.6, 134, 148.5; **Anal.** Calcd for C\(_{25}\)H\(_{20}\)N\(_6\)O: C, 71.41; H, 4.79; N, 19.99; Found: C, 71.39; H, 4.77; N, 20.00 %.

**1,3-Diphenyl-2,2-bis(4-phenyl-1H-1,2,3-triazol-1-yl)propan-1-one (27b)**

**Yield:** 87%; pale yellow solid; **mp:** 144-149 °C; **IR** (neat, cm\(^{-1}\)); \(\nu_{\text{max}}\) 752, 1162, 1434, 1692, 1738, 2937; **\(^1\)H NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 3.95 (d, \(J = 3.2\) Hz, 2H), 6.84-6.88 (m, 2H), 7.18-7.75 (m, 20H); **\(^13\)C NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 42.3, 83.7, 118.6, 125.8, 127.9, 128.5, 128.7, 128.8, 129.0, 129.2, 130.3, 131.1, 133.7, 135.0,
3,4-Dihydro-2,2-bis(4-phenyl-1H-1,2,3-triazol-1-yl)naphthalen-1(2H)-one (27c)

Yield: 85%; pale yellow solid; mp: 166-168 °C; IR (neat, cm⁻¹): νmax 685, 783, 1058, 1441, 1695, 1745, 2931; ¹H NMR (200 MHz, CDCl₃): 2.68-2.76 (m, 1H), 2.85-2.91 (dt, J = 5.04, 4.58 and 17.86 Hz 1H), 3.31-3.37 (m, 1H), 3.43-3.50 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): 24.8, 32.0, 81.1, 121.2, 125.8, 125.9, 127.7, 128.8, 129.0, 129.5, 130.1, 130.5, 134.5, 135.1, 138.8, 141.4, 148.1, 184.1; Anal. Calcd for C₂₆H₂₀N₆O: C, 72.20; H, 4.66; N, 19.43; Found C, 72.20; H, 4.65; N, 19.44 %; LCMS (ESI) m/z Calcd for C₂₆H₂₀N₆Na [M + Na]⁺, 455.1699; found, 455.12.

3,4-Dihydro-2,2-bis(4-phenyl-1H-1,2,3-triazol-1-yl)naphthalen-1(2H)-one (27d)

Yield: 85%; pale yellow solid; mp: 152-154 °C; IR (neat, cm⁻¹): νmax 691, 764, 1070, 1452, 1689, 1735, 2940; ¹H NMR (200 MHz, CDCl₃): δ 3.71 (s, 1H), 7.18-7.51 (m, 13H), 7.77 (s, 2H), 7.85 (s, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 30.1, 99.2, 126.1, 127.8, 134.2, 136.9, 147.3, 155.8, 198.4; Anal. Calcd for C₂₅H₁₈N₆O: C, 71.76; H, 4.66; N, 19.44 %.

1-Phenyl-2,2-bis(4-phenyl-1H-1,2,3-triazol-1-yl)butan-1-one (27e)

Yield: 87%; pale yellow solid; mp: 169-171 °C; IR (neat, cm⁻¹): νmax 751, 1120, 1469, 1698, 1745, 2930; ¹H NMR (200 MHz, CDCl₃): δ 0.96 (t, J = 7.1 Hz, 3H), 2.40 (q, J = 7.2 Hz 2H), 7.22-7.34 (m, 14H), 7.63 (s, 2H), 8.02 (s, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 5.8, 20.5, 93.9, 127.8, 129.2, 129.6, 130.3, 132.6, 133.7, 148.4; Anal. Calcd for C₂₆H₂₀N₆O: C, 71.87; H, 5.10; N, 19.34; Found: C, 71.85; H, 5.11; N, 19.31 %.

1-Phenyl-2,2-bis(4-phenyl-1H-1,2,3-triazol-1-yl)pentan-1-one (27f)

Yield: 86%; pale yellow solid; mp: 175-178 °C; IR (neat, cm⁻¹): νmax 675, 1254,
1478, 1694, 1742, 2967; \textbf{\textsuperscript{1}H NMR} (200 MHz, CDCl\textsubscript{3}): $\delta$ 1.12 (t, $J = 7.0$ Hz, 3H), 1.42 (m, 2H), 2.41 (m, 2H), 7.22-7.48 (m, 13H), 7.65 (s, 2H), 8.87 (m, 2H); \textbf{\textsuperscript{13}C NMR} (50 MHz, CDCl\textsubscript{3}): $\delta$ 5.8, 20.5, 93.9, 127.8, 129.2, 129.6, 130.3, 132.6, 133.7, 134.0 148.4; \textbf{Anal.} Calcd for C\textsubscript{27}H\textsubscript{24}N\textsubscript{6}O: C, 72.30; H, 5.39; N, 18.74; Found: C, 72.32; H, 5.38; N, 18.72%.

4.2.6 References:


15 Minisci, F.; Galli R., F. R. Patent 1, 350, 360 (A) \textbf{1964}.


