CHAPTER-1

Pd/C mediated alkynylation of N-heterocycles
1.1. Introduction

The Pd-catalysed alkynylation of aryl/hetaryl halides via C–C bond-formation (Sonogashira coupling) has wide applications in synthetic and organometallic chemistry. Earlier in 1975, this type of transition metal catalysed cross-coupling reactions was reported independently by Heck\(^1\) and Cassar\(^2\). Heck’s procedure was based on the arylation or alkenylation of alkenes, employing a phosphane-palladium complex as a catalyst and triethylamine or piperidine as a base and solvent, while, Cassar’s procedure involved the use of a phosphane-palladium catalyst in combination with sodium methoxide as a base and DMF as solvent. Both of these methods required high temperature ~100 °C. Later, in the same year, Sonogashira and Hagihara reported that addition of a catalytic amount of copper(I) iodide greatly accelerates the reaction, and thus enabling the alkynylation reaction to perform at room temperature (Scheme 1.1).\(^3\) Since its discovery in 1975, the methodology is vastly applied in the grounding of precursors for bioactive molecules, natural products, polymers and molecular electronics.
Scheme 1.1

The copper-cocatalyzed Sonogashira reaction is believed to take place through two independent catalytic cycles as shown in Scheme 1.2.\textsuperscript{4-6} The Pd-catalyst initially generates one active Pd species Pd\textsuperscript{0}L\textsubscript{2}. The next step is oxidative addition of R\textsuperscript{1}-X (R\textsuperscript{1}= aryl, hetaryl, vinyl; X = I, Br, Cl, OTf) to the active Pd-species, which is facilitated if X = I or OTf. The Pd-cycle then connects with the copper cycle (the Cu-cycle). Then, transmetalation occurs with the copper acetylide (C) formed in the Cu cycle to generate a Pd-alkyne (B) complex, which gives the final coupled alkyne after trans/cis isomerisation and reductive elimination with regeneration of the catalyst. In the copper catalysed cycle, the amine base abstracts the Cu(I) salt forms a \pi-alkyne- Cu complex, thus makes the alkyne proton more acidic for easier abstraction. The amine base then abstracts proton from the terminal alkyne and forms the copper acetylide C, which is then involved in the Pd-catalysed cycle.
Scheme 1.2. Mechanism of Sonogashira coupling

Inspite of the versatile applicability of the Sonogashira coupling methodology, the requirement of precious palladium and expensive ligands often hampers the large scale accessibility of the process. However, the drawback was overcome by the use of heterogeneous palladium catalysts, which are easily recovered from the reaction mixture and also eliminates the chance of contamination of the product by the metal. Thus, the heterogeneous catalytic process is found to be more cost-effective when compared with the homogeneous catalyst.\textsuperscript{7} [It is worth to mention that, the heterogeneous palladium on charcoal or activated carbon (Pd/C), which was previously used only for hydrogenation\textsuperscript{8} has gained attention of the chemists for performing these types of cross-coupling reactions. Although this is a “ligand-free” species, in some cases, triphenylphosphine is added to the reaction medium and a palladium-phosphane complex is formed. The use of
Pd/C catalysts have successfully eradicated the drawbacks arising from expensive Pd-catalysts. The use of Pd/C also resulted in significant improvement of the reaction rate and avoidance of expensive ligands. Moreover Pd/C is a cheap and air stable catalyst which can be easily recovered from the reaction mixture and is recyclable. All these properties of Pd/C have made it a versatile catalyst for Sonogashira coupling and its development and applicability were discussed in several reviews.

1.2. Types of palladium/carbon (Pd/C)

The solid support of heterogeneous Pd-catalysts plays significant role in the recovery, refining and recycling of the catalyst, along with increase in rate, selectivity and reproducibility of the reaction.\textsuperscript{9-11} The cheap and commercially available activated carbons are generally used for solid supports as they are stable under acidic and basic conditions and possess much higher surface area. It is also less abrasive and thus can be easily recovered by simple filtration process. The availability of these distinct features in the Pd/C catalysts has prompted chemists to use it in various cross-coupling reactions. Nowadays, Pd/C catalysts are effectively used in synthetic organic chemistry for preparation of wide variety of compounds.

[Depending on the distribution of Pd on carbon, Pd/C catalysts are categorized into three categories namely, uniform, eggshell and thickshell (Figure 1). In uniform category, Pd is homogeneously dispersed, while in
eggshell Pd is dispersed only on the surface of the solid support within 50–150 nm depths. Another intermediate category is the thick shell where Pd is distributed to depth of 200–500 nm from the surface.]

Figure 1. Distribution of Pd in Pd/C catalysts
Commercially available Pd/C catalysts contain Pd ranging from 1% to 20%. The materials can contain up to 50% water. Another advantageous point of Pd/C is that it can be used with or without additional ligands. Pd/C catalyzed cross-coupling reactions can be carried out in organic solvents or organic solvent/water mixtures. In few cases use of ionic liquids\textsuperscript{12-15} were reported, while some cases were also reported where reactions were carried out under solvent-free conditions.

1.3. Mechanism of Palladium Carbon mediated alkynylation:
The reaction proceeds through generation of an active Palladium(0) species. The active Palladium (0) species is generate \textit{in situ} from the minor portion of the bound palladium Carbon via a Palladium leaching process in the reaction medium. In presence of Triphenyl phosphine, the leached Palladium becomes an active Palladium (0) species by interacting with phosphine ligands i.e. a soluble Palladium (0)– Triphenyl phosphine complex is formed which actually catalyzes the Carbon–Carbon bond forming
reaction in solution. [The catalytic cycle therefore movement in solution rather than on the surface and at the end of the reaction, re-precipitation of pd occurs on the surface of the C. Once generated, the soluble Palladium (0)–Triphenyl phosphine complex, undergoes oxidative adding together with the HX to give the organopalladium(2) species Z, which then facilitates the stepwise formation of Carbon –Carbon bond via (i) trans organometallation with Cu acetylide generated in situ from Copper iodide and the 1-alkyne followed by (ii) reductive elimination of Palladium (0) to afford alkynylsubstituted arene] (Figure 2).

**Figure 2.** Possible mechanism for Palladium Carbon catalysed alkynylation of ArX

**1.4. Pd/C catalysed Sonogashira coupling reaction of N-heterocycles:**
1.4.1. *In anhydrous media:*

Palladium Carbon –Triphenyl phosphine –Copper iodide has been developed as an proficient catalytic system for Sonogashira reaction in anhydrous organic solvents. For example, 2-bromopyridine (1)\(^{16}\) coupled with 2-(3-hydroxy-3-methyl-but-1-ynyl)- substituted pyridines 2 and 4 in presence of this catalytic system to form dipyrindylethylenes 3 and 5 (Scheme 1.3).

\[
\begin{align*}
\begin{array}{c}
\text{Pyridine} + \text{Pyridine} \\
\text{N} \quad \text{Br} + \text{N} \quad \text{CMe} \quad 2 \quad \text{OH} \\
Pd/C (0.8 \text{ mol\%}) \quad \text{PPh}_3 \quad \text{CuI} \\
\text{Et}_3\text{N}, \text{MeCN} \\
\text{NaOH, reflux, 36h} \\
77\% \\
\end{array}
\end{align*}
\]

**Scheme 1.3**

Sonogashira coupling of s-triazine 6\(^{17}\) with alkyne 7 was also successfully carried out affording compound 8 by using Pd/C catalysis with chloro as the leaving group (Scheme 1.4).

![Scheme 1.3](image-url)
A selective coupling with phenyl acetylene in the 4-position of 5-bromo-4-chloropyrimidine 9 was reported from our group (Scheme 1.4).\textsuperscript{18} The remaining bromo substituent 10 could be further alkynylated by a second alkyne by a subsequent Sonogashira coupling.

Bates and co-workers reported a Pd/C-catalyzed Sonogashira coupling of methyl 2-chloronicotinate (11) with 2-propynyloxytetrahydropyran in the synthesis of (±)-tashiromine, without using phosphpine ligand.\textsuperscript{19} The pyridyl alkyne 12 was obtained in 83% yield (Scheme 1.5).
Scheme 1.6

The Pd/C catalysed Sonogashira couplings were also utilized for the synthesis of furoquinolines with wide range of pharmacological properties.\textsuperscript{20,21} [The reaction is a 2-step method, the step 1 being the Sonogashira coupling of the HX with a 1-alkyne, which then undergoes \textit{in situ} cyclization with the neighbouring oxygen to form the furan ring. Thus, the coupling of iodoquinoline derivative 13 with a variety of 1-alkynes afforded furo[3,2-c]quinolines 14 regioselectively in good to tremendous yields] (Table 1).\textsuperscript{22}

\textbf{Table 1: Pd/C-based Synthesis of Furo[3,2-c]quinolines}

<table>
<thead>
<tr>
<th>( \mathbf{R} )</th>
<th>( \mathbf{Y} )</th>
<th>( \mathbf{Z} )</th>
<th>( \text{Yield (%)} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(OH)Me\textsubscript{2}</td>
<td>CO\textsubscript{2}Me</td>
<td>F</td>
<td>83</td>
</tr>
<tr>
<td>CH(OH)Me</td>
<td>CO\textsubscript{2}Me</td>
<td>F</td>
<td>85</td>
</tr>
<tr>
<td>C(OH)Me\textsubscript{2}</td>
<td>Ph</td>
<td>H</td>
<td>70</td>
</tr>
<tr>
<td>(CH\textsubscript{2})\textsubscript{2}OH</td>
<td>Ph</td>
<td>H</td>
<td>72</td>
</tr>
</tbody>
</table>

Similar kind of coupling–cyclization strategy using palladium/carbon catalyst was adapted in the synthesis of 2-substituted pyrroloquinolines. Thus, the reaction of 8-iodoquinoline derivatives (15) with a different 1-
alkynes in the presence of 10% Palladium carbon – Triphenyl phosphine–Copper iodide in EtOH furnished 2-substituted 6-oxopyrrolo[3,2,1-ij]quinolines 16 in good yields (Table 2).23

Table 2: Palladium Carbon based synthesis of pyrrolo[3,2,1-ij]quinolines

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>85</td>
</tr>
<tr>
<td>(CH₂)₂OH</td>
<td>85</td>
</tr>
<tr>
<td>CH(OH)CH₃</td>
<td>95</td>
</tr>
<tr>
<td>(CH₂)₂CN</td>
<td>75</td>
</tr>
<tr>
<td>(CH₂)₃OH</td>
<td>81</td>
</tr>
</tbody>
</table>

Isocoumarins have also been prepared by Sonogashira coupling and then cyclization from suitable o-(1-alkynyl)benzoic acids or esters, following two-step procedures with preliminary isolation of the Sonogashira product and cyclization with electrophilic reagents.24,25 An alternate coupling-cyclization process for preparation of isocoumarin 18 is also depicted in
literature which involve the one-pot procedure starting from acid 17 employing palladium on charcoal in the presence of pph$_3$ and Cu(I) iodide.$^{26}$

\[
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{Me}
\end{array}
\xrightarrow{10\% \text{Palladium Carbon, PPh}_3, \text{CuI, Et}_3\text{N, Ethanol, } 80^\circ\text{C}}
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{Me}
\end{array}
\xrightarrow{\text{Me}}
\begin{array}{c}
\text{O} \\
\text{OH}
\end{array}
\]

Scheme 1.7

Palladium/charcoal combined with a resin-bound tertiary amine (Amberlite IRA-67), can be employed for the copper-cocatalyzed coupling of N-protected propargyl amines to nucleoside e.g. 5-iodouracil, 5-iodocytosine, and 2-bromoguanine.$^{27}$ One such example is the cross-coupling reaction of iodinated dideoxyuridine derivative 19 and propargylated trifluoroacetamide 20 to give compound 21 (Scheme 1.7).

\[
\begin{array}{c}
\text{NH} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{O}
\end{array}
\xrightarrow{10\% \text{Pd/C, CuI, amberlite-IRA-67, DMF, } 50^\circ\text{C, 69\%}}
\begin{array}{c}
\text{F}_3\text{C} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{NH}
\end{array}
\]

Scheme 1.8

3-Alkynylpyrazolo[1,5-a]pyrimidines 23 have been synthesized from the corresponding 3-iodopyrazolopyrimidines 22 and propargyl alcohol using the Sonogashira methodology, using palladium on charcoal as palladium source (Scheme 1.8).$^{28}$
Scheme 1.9

1.4.2. In organic solvent/water mixture

Organic solvent/water mixtures provide a more convenient and efficient medium for Pd/C catalysed reaction with Potassium Carbonate as base in most cases. Thus, Pd/C in DME water medium was used to synthesize enantiomerically pure (S)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)-pyridine \( \text{26} \) (SIB-1508Y) as a novel enantiopure nicotinic acetylcholine receptor agonist from bromopyridine \( \text{24} \). The corresponding Sonogashira product \( \text{25} \) was treated with NaH in toluene to afford \( \text{26} \) (Scheme 1.5).

Scheme 1.10

Pd/C was found to be efficacious than other commonly used homogeneous Palladium(II) or Palladium (0) catalysts [Pd(PPh\(_3\))\(_2\)Cl\(_2\), Palladium tetrakise, and Palladium acetate] in many cases e.g. Liebscher and co-worker reported the synthesis of \( \omega \)-functionalized alkynylpyrazolo[1,5-
a]pyrimidine 28 as potential calcineurin inhibitors was achieved from 3-iodopyrazolo[1,5-a]pyrimidines 27 in presence of Palladium Carbon-Triphenyl phosphene-Copper iodide system (Scheme 1.6).  

![Scheme 1.11](image)

**Scheme 1.11**

Reports are also available where coupling reaction failed with Pd(PPh$_3$)$_2$Cl$_2$ and CuI, but 97% yield of the product was obtained with Pd/C, PPh$_3$, and CuI. For example, dimethylaminopropynyl chain was introduced into a pyrazole ring (compound 30) via Pd/C-catalyzed Sonogashira coupling of 3-iodopyrazole 29 with N,N-dimethylpropargylamine (Scheme 1.7).  

![Scheme 1.12](image)

**Scheme 1.12**

Another application of the Pd/C-mediated methodology in water medium was demonstrated by the preparation of 2-alkynylquinolines 32 bearing antiretroviral properties (Table 3).  

Process that involved the coupling of 2-chloroquinoline (31) with terminal
alkynes was superior as the catalysts are recyclable and it also discards the use of expensive organic cosolvents. The experimental regioselectivity in the alkynylation of 2,4-dichloroquinoline at the 2 position could be explained by (i) the higher reactivity of the chloro group at the 2 over the 4 position on the quinoline ring and (ii) intramolecular coordination of the quinoline nitrogen to the pd after formation of the quinoline–pd–Cl complex.

**Table 3** Synthesis of 2-Alkynylquinolines

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(OH)(CH$_3$)$_2$</td>
<td>80</td>
</tr>
<tr>
<td>(CH$_2$)$_2$OH</td>
<td>53</td>
</tr>
<tr>
<td>(CH$_2$)$_3$OH</td>
<td>61</td>
</tr>
<tr>
<td>n-butyl</td>
<td>65</td>
</tr>
<tr>
<td>(CH$_2$)$_5$Me</td>
<td>62</td>
</tr>
</tbody>
</table>

Till now several examples are given where the Sonogashira coupling was carried out in organic solvents or in a mixture of organic solvent and water. But, nowadays a strong effort towards green chemistry has resulted the Sonogashira coupling in water medium using the same Pd/C catalyst. In one such effort, the Sonogashira reaction of iodo benzene (33) with phenylacetylene was carried out in water using Palladium Carbon as catalyst.
and surfactants as additives. Moreover, the reaction does not require CuI salt, phosphine ligand, amine base or an inert atmosphere. Cationic surfactants were found to promote the reaction yielding the alkynyl derivative 34 (Scheme 1.8).\(^{36}\)

![Scheme 1.13](image)

**Scheme 1.13**

Another report shows, a novel and efficient [synthesis of 2-benzylimidazo[1,2-\(a\)]pyrimidines via Pd/C-mediated copper-free Sonogashira coupling in water. The alkyne 2-imino-1-(2-propynyl)pyrimidine (36) was synthesized by reaction of 2-aminopyrimidine (35) with propargyl bromide in refluxing acetonitrile. The alkyne 36 then reacted with aryl iodide in presence of Pd/C, potassium carbonate (K\(_2\)CO\(_3\)) as base in water medium to afford 2-benzylimidazo[1,2-\(a\)]pyrimidines] (37) (Table 4).\(^{37}\)

**Table 4** Synthesis of 2-benzylimidazo[1,2-\(a\)]pyrimidines
Conclusion:
The alkynylation of aryl and hetaryl halides by pd catalysis is an essential method for synthetic organic chemists. But, it is still challenging
when used for industrial applications. The major problem associated with this process is the elimination of metallic pd from the product. Because of the easy recovery of pd/C, the use of this catalyst could be a potential solution to this problem in addition, due to the recyclability of the catalysts, the pd/C-mediated process can be an attractive and cheaper substitute to other expensive palladium catalysts. In the next chapters we will discuss that how efficiently the Pd/C catalyst has been utilized for alkynylation of thienopyrimidine, indazole, pyrazole and olanzapine.

References:


