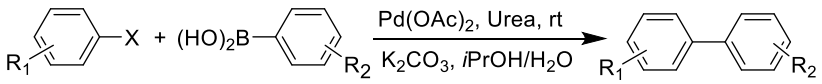
# Chapter 2

## *Development of a mild and efficient methodology for palladium catalyzed Sonogashira cross coupling reaction*

**Abstract**: This chapter discloses the utilization of urea as a mild and efficient promoter for palladium-catalyzed Sonogashira cross-coupling reaction of aryl halides and terminal alkynes. The system serves as an excellent alternative to various ligands assisting system and is highly flexible for both aromatic and aliphatic alkynes under mild reaction conditions.

## 2.1. Introduction

Palladium catalyzed Sonogashira cross-coupling reaction serves as an important methodology for construction of $C_{sp2}$-$C_{sp}$ bonds. It finds wide application in synthesis of pharmaceuticals, natural products and various other organic compounds [1-3]. Traditionally, use of copper salt as a co-catalyst and amine as base is common in Sonogashira reaction [4]. However, the use of copper result in the formation of Glaser type coupling which decreases the product efficiency [5]. Consequently, various modifications has been made, for instance development of highly active palladium complexes with phosphine [6], NHC [7], Schiff base [8], palladacycles [7] etc. or use of other metal salts like AuI [9], $Ag_2O$ [10], $ZnCl_2$ [11], and $R_3Sn$ [12] as co-catalyst. Although, ligand-based palladium complexes show excellent catalytic activity, their uses leads to significant limitations regarding high cost, availability, stability, and difficulty in isolation of product. Moreover, they require additional synthetic methodologies and sometime many of these ligands are air and moisture sensitive and therefore, the reactions are required to perform in an inert atmosphere. Thus, researchers are trying to develop simple, efficient, stable, cost-effective and environmentally friendly catalytic system for the coupling reaction. Some interesting works has been reported in the literature where common laboratory chemicals and reagents such as sodium sulfate [13], PEG [14] etc. were successfully utilized as promoters for the Sonogashira cross-coupling reaction under milder conditions. Urea is another commonly used cheap and easily available chemical which possess great complexing ability with different metal ions [15]. The effectiveness of urea as promoter was observed in $Pd(OAc)_2$ catalyzed Suzuki-Miyaura cross-coupling reaction (Scheme 2.1) [16]. Considering these aspects, in this chapter, we examined the effect of urea in Pd catalyzed Sonogashira cross-coupling reaction of aryl halide and terminal acetylene at room temperature.




**Scheme 2.1**: $Pd(OAc)_2$/Urea catalysed Suzuki-Miyaura cross-coupling reaction

## 2.2. Experimental

### 2.2.1. General experimental procedure

In a 50 mL round bottom flask, a mixture of aryl halide (0.5 mmol), acetylene (0.75 mmol), $Pd(OAc)_2$ (1 mol %), urea (0.25 mmol) and $K_2CO_3$ (1.5 mmol) were mixed in

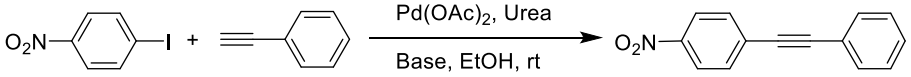
EtOH (4 mL) and stirred at room temperature. The reaction was monitored by TLC and after completion, the reaction mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layer was washed with brine (20 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using *n*-hexane as eluent to obtain the corresponding diarylalkyne. The desired products are characterized by comparing $^1H$ and $^{13}C$ NMR data with authentic samples.

## 2.3. Results and Discussion

### 2.3.1. Optimization of catalytic system for Sonogashira coupling reaction

Initially, the catalytic activity of $Pd(OAc)_2$/urea system has been investigated in Sonogashira cross-coupling reaction using 4-iodonitrobenzene (0.5 mmol) and phenylacetylene (0.75 mmol) as the model substrates with $K_2CO_3$ as base in EtOH (Table 2.1**)**. It is seen that the coupling reaction proceeds in good yield with $Pd(OAc)_2$ (1 mol%) and urea (1 mmol) (Table 2.1, entry 1). The formation of the desired diarylalkyne was confirmed by its NMR spectra. $^1H$ NMR spectra with peaks at 8.22 (d, 2H) is due to aromatic ring protons adjacent to $–NO_2$ group and peaks at 7.68-7.66 (m, 2H), 7.57-7.55 (m, 2H) and 7.40-7.38 (m, 3H) corresponds to other aromatic ring protons. Further confirmation was achieved by its $^{13}C$ NMR data with peaks at 94.8 and 87.2 for two acetylene carbon and peaks at δ ppm 147.0, 132.3, 131.9, 130.3, 129.3, 128.6, 123.7, 122.1 is due to aromatic ring carbon.

**Table 2.1**: Screening of catalyst loading on Sonogashira coupling of 4-iodonitrobenzene and phenylacetylene [a]




| Entry | Catalyst (mol %) | Urea (mmol) | Time (h) | Yield (%) [b] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (1) | 1 | 3 | 98 |
| 2 | $Pd(OAc)_2$ (0.5) | 1 | 7 | 45 |
| 3 | $Pd(OAc)_2$ (1) | 0.5 | 3 | 97 |
| 4 | $Pd(OAc)_2$ (1) | 0.25 | 3 | 96 |
| 5 | $Pd(OAc)_2$ (1) | 1.5 | 3 | 98 |
| 6 | $Pd(OAc)_2$ (1) | - | 12 | 60 |
| 7 | $PdCl_2$ (1) | 0.25 | 4 | 50 |

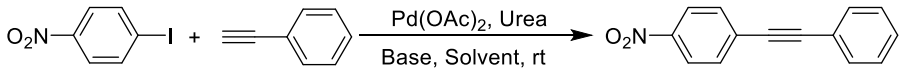
[a] Reaction conditions: 4-iodonitrobenzene (0.5 mmol), phenylacetylene (0.75 mmol), $K_2CO_3$ (1.5 mmol), EtOH (4 mL) at rt. [b] Isolated yield.

Thereafter, the reaction was screened by varying the amount of $Pd(OAc)_2$ and urea (Table 2.1, entries 2-5). On decreasing the amount of $Pd(OAc)_2$ to 0.5 mol%, considerable decrease in cross-coupling product was observed (Table 2.1, entry 2). It was observed that the reaction give optimum yield of desired product with 0.25 mmol urea (Table 2.1, entry 4). On increasing the amount of urea to 1.5 mmol, no remarkable difference in product yield was observed (Table 2.1, entry 5). However, the yield of the product sharply reduced to 60% in absence of urea, which signifies the effect of urea in the catalytic system (Table 2.1, entry 6). Generally, urea acts as monodentate ligand to form stable metal complexes [15]. As a result, in the present protocol, an *in situ* palladium-urea complex might form which enhances the Sonogashira cross-coupling reaction. The compatibility of the reaction system was examined for $PdCl_2$, but desired efficiency of the reaction was not achieved (Table 2.1, entry 7).This may be due to the difference in complexing ability of both the palladium salt [$Pd(OAc)_2$ and $PdCl_2$] with urea. Consequently, further studies of the catalytic system was done with $Pd(OAc)_2$ (1 mol%) and urea (0.25 mmol).

### 2.3.2. Optimization of solvent and base for Sonogashira coupling reaction

In the next step, the effect of various solvents and bases on the cross-coupling reaction was investigated (Table 2.2).

**Table 2.2**: Screening of efficiency of solvent and base for coupling of aryl iodide and phenylacetylene [a]




| Entry | Solvent | Base | Time (h) | Yield (%) [b] |
|---|---|---|---|---|
| 1 | EtOH | $K_2CO_3$ | 3 | 96 |
| 2 | $H_2O$ | $K_2CO_3$ | 24 | 40 |
| 3 | *i*-PrOH | $K_2CO_3$ | 5 | 50 |
| 4 | EtOH/ $H_2O$ | $K_2CO_3$ | 6 | 60 |
| 5 | *i*-PrOH/ $H_2O$ | $K_2CO_3$ | 6 | 40 |
| 6 | EtOH | $Cs_2CO_3$ | 3 | 96 |
| 7 | EtOH | NaOH | 4 | 50 |

[a] Reaction conditions: 4-iodonitrobenzene (0.5 mmol), phenylacetylene (0.75 mmol), $Pd(OAc)_2$ (1 mol %), urea (0.25 mmol), base (1.5 mmol), solvent (4 mL) at rt. [b] Isolated yield.

As already observed in Table 2.1, entry 4, superior catalytic performance was observed in EtOH as the reaction medium (Table 2.2, entry 1). Use of water for the

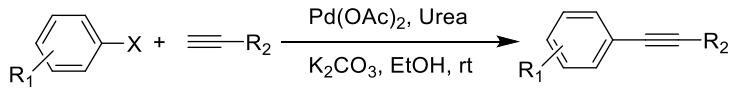
coupling reaction decreases the catalytic activity. This may be because of the insolubility of low polar reactant in the reaction medium resulting in weaker interaction with the catalytic species (Table 2.2, entry 2). Other solvent system such as *i*-PrOH and aqueous alcoholic solvents also result in lower yield of desired product (Table 2.2 entries 3-5). Since EtOH is environmentally safe, economically viable and easily accessible, it serves as an appropriate reaction medium for the present catalytic system. The reaction was screened for different inorganic bases such as $K_2CO_3$, $Cs_2CO_3$ and NaOH (Table 2.2 entries 1, 6 & 7). Excellent catalytic activity was observed using $K_2CO_3$ and $Cs_2CO_3$ (Table 2.2 entries 1 & 6 vs 7). But considering the low cost and greater availability, $K_2CO_3$ was used for the coupling reaction.

### 2.3.3. Substrate scope for Sonogashira coupling reaction

To evaluate the scope and limitations of the present reaction system, we examine the cross-coupling reaction of a wide range of electronically diverse aryl halides and terminal acetylenes using the optimized reaction conditions (Table 2.3). The $Pd(OAc)_2$/urea system was effective towards most of the electron withdrawing and electron donating aryl halides. The catalytic system delivers excellent yield for both electron donating and withdrawing *para*- and *meta*- substituted aryl iodides (Table 2.3, entries 1,2 & 5,6). However, aryl iodides with methoxy substituents gave slightly lower yield of the desired product in comparison to methyl substituents (Table 2.3, entry 2 vs 3). Again steric factor affects the reaction efficiency, as we have seen that 2-iodonitrobenzene results in very low conversion of cross-coupling product (Table 2.3, entry 7). Although electron donating aryl halides reacts with phenylacetylene with excellent reactivity, 4-aminoiodobenzene provides poor yield of cross-coupling product (only 50% yield) (Table 2.3, entry 4). This is due to the greater tendency of nitrogen to release its non-bonding electron-pair which might coordinate with palladium and as a result decreases its reactivity towards cross-coupling reaction. No significant difference in catalytic efficiency was observed for phenylacetylene containing electron donating group (Table 2.3, entry 9). The coupling of aryl halides with aliphatic alkynes provides appreciable yield of alkynyl derivatives (Table 2.3, entries 10-14). The activity of the catalytic system was examined for coupling of aryl bromides. Excellent yield of desired product was obtained for bromobenzene and electron donating methyl group at 60° C. (Table 2.3, entries 15-17). Electron withdrawing aryl bromide *i.e. p*-nitrobromobenzene affords lower yield of desired product (Table 2.3, entry 18). Again coupling of 4-

bromotoluene with aliphatic alkynes was performed, moderate yield of cross-coupled product was achieved (Table 2.3, entry 19).

**Table 2.3**: Sonogashira coupling of aryl halides with different terminal acetylenes [a]



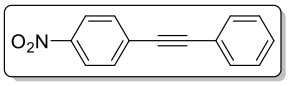

| Entry | $R_1$ | $R_2$ | X | Time (h) | Yield (%) [b] |
|---|---|---|---|---|---|
| 1 | 4-$NO_2$ | $C_6H_5$ | I | 3 | 96 |
| 2 | 4-Me | $C_6H_5$ | I | 4 | 98 |
| 3 | 4-OMe | $C_6H_5$ | I | 5 | 80 |
| 4 | 4-$NH_2$ | $C_6H_5$ | I | 8 | 50 |
| 5 | 3-Me | $C_6H_5$ | I | 3 | 92 |
| 6 | 3-$NO_2$ | $C_6H_5$ | I | 4 | 90 |
| 7 | 2-$NO_2$ | $C_6H_5$ | I | 8 | 40 |
| 8 | H | $C_6H_5$ | I | 3 | 98 |
| 9 | 4-Me | 4-Me$C_6H_5$ | I | 3 | 97 |
| 10 | 4-Me | $C_4H_9$ | I | 4 | 90 |
| 11 | 4-Me | Cyclohexyl | I | 4 | 90 |
| 12 | H | $C_{10}H_{21}$ | I | 5 | 80 |
| 13 | H | $C_4H_9$ | I | 4 | 95 |
| 14 | H | Cyclohexyl | I | 4 | 93 |
| 15 | H | $C_6H_5$ | Br | 6 | 95 [c] |
| 16 | 4-Me | 4-Me$C_6H_5$ | Br | 6 | 85 [c] |
| 17 | 4-Me | $C_6H_5$ | Br | 6 | 95 [c] |
| 18 | 4-$NO_2$ | $C_6H_5$ | Br | 8 | 50 [c] |
| 19 | 4-Me | $C_4H_9$ | Br | 8 | 70 [c] |

[a] Reaction conditions: aryl halide (0.5 mmol), acetylene (0.75 mmol), $Pd(OAc)_2$ (1 mol%), urea (0.25 mmol), $K_2CO_3$ (1.5 mmol), EtOH (4 mL), rt. [b] Isolated yield
[c] 60 °C

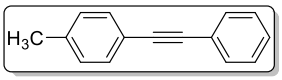
## 2.4. Conclusions

In summary, we have described an efficient Sonogashira cross coupling reaction under amine and copper free conditions using $Pd(OAc)_2$ and urea under aerobic condition. The present synthetic approach allowed preparation of diverse range of alkynyl derivatives in excellent yields. Moreover, this work highlights the use of low cost, mild and easily available effective promoter, which makes this catalytic system a promising candidate for the Sonogashira cross-coupling reaction.

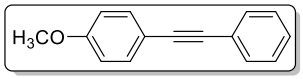
**2.5. Analytical data of the synthesized alkynyl derivatives.**



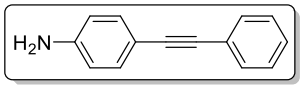
**1-Nitro-4-(2-phenylethynyl)benzene (Table 2.3, entry 1):** Yellow Solid, m.p. 119-121 °C, **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.22 (d, 2H, *J* = 8.8 Hz), 7.68-7.66 (m, 2H,), 7.57-7.55 (m, 2H), 7.40-7.38 (m, 3H) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 147.0, 132.3, 131.9, 130.3, 129.3, 128.6, 123.7, 122.1, 94.8, 87.2 ppm.



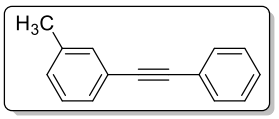
**1-Methyl-4-(2-phenylethynyl)benzene (Table 2.3, entry 2):** White solid, m.p. 68-70 °C, **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.56-7.50 (m, 2H), 7.42 (d, 2H, *J* = 7.7 Hz), 7.36-7.31 (m, 3H), 7.15 (d, 2H, *J* = 7.7 Hz), 2.36 (s, 3H) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 138.4, 132.4, 131.6, 129.2, 128.5, 128.1, 123.5, 120.2, 89.6, 88.8, 21.6 ppm.



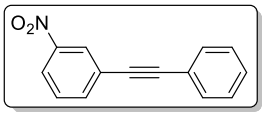
**1-Methoxy-4-(2-phenylethynyl)benzene** (**Table 2.3 entry 3**)**:** White solid, m.p. 79-81 °C, **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.51-7.45 (m, 4H), 7.32-7.30 (m, 3H), 6.86 (d, 2H, *J* = 8.7 Hz), 3.82 (s, 3H) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 159.7, 133.1, 131.5, 128.4, 128.0, 123.7, 115.4, 114.1, 89.9, 89.4, 55.4 ppm.



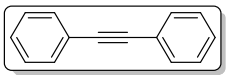
**1-Amino-4-(2-phenylethynyl)benzene (Table 2.3, entry 4):** Yellow Solid, m.p. 125-127 °C., **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.46-7.42 (m, 2H), 7.22-7.12 (m, 4H,), 6.49-6.47 (m, 2H), 4.13 (s, 2H) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 147.1, 132.6, 131.9, 129.1, 128.4, 128.1, 123.2, 118.1, 89.9, 88.7 ppm.



**1-Methyl-3-(2-phenylethynyl)benzene** (**Table 2.3 entry 5**)**:** Colourless liquid, **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.53-7.51 (m, 2H), 7.36-7.33 (m, 4H), 7.25-7.21 (m, 2H), 7.14 (d, 1H, *J* = 7.3 Hz), 2.35(s, 3H) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 138.1, 134.5, 132.6, 131.7, 129.2, 128.8, 128.4, 128.3, 128.2, 123.4, 89.6, 89.1, 21.3 ppm.



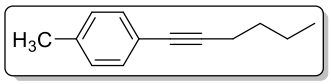
**1-Nitro-3-(2-phenylethynyl)benzene** (**Table 2.3 entry 6**)**:** Yellow gum, **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.35 (s, 1H), 8.15 (d, 1H, *J* = 8.2 Hz), 7.80 (d, 1H, *J* = 7.7 Hz), 7.56-7.48 (m, 3H), 7.38-7.34 (m, 3H) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 148.2, 137.3, 131.8, 129.4, 129.1, 128.6, 126.4, 125.2, 122.9, 122.2, 92.0, 86.9 ppm.



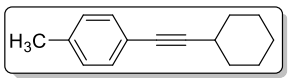
**Diphenylacetylene** (**Table 2.3 entry 8**)**:** White Solid, m.p. 54-56 °C, **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.56-7.54 (m, 4H), 7.38-7.34 (m,

6H) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 131.7, 128.4, 128.3, 123.3, 89.4 ppm.

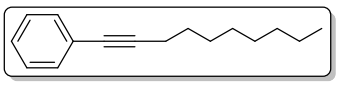
**1-Methyl-4-[2-(*p*-tolyl)ethynyl]benzene** (**Table 2.3 entry 9):** White solid, m.p. 126-128 °C, **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.39 (m, 4H), 7.14-7.12 (m, 4H), 2.35 (s, 6H) ppm.**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 138.2, 131.5, 129.3, 120.4, 88.9, 87.2, 21.5 ppm.



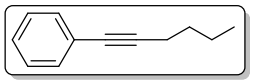
**1-(Hex-1-yn-1-yl)-4-methylbenzene** (**Table 2.3 entry 10**)**:** Yellow liquid, **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.29-7.25 (m, 2H), 7.08-7.06 (m, 2H), 2.41-2.37 (m, 2H), 2.32 (s, 3H), 1.60-1.46 (m, 4H), 0.96-0.92 (m, 3H) ppm.**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 137.4, 131.4, 129.3, 121.0, 89.6, 87.2, 30.9, 22.1, 21.4, 19.2, 13.7 ppm.



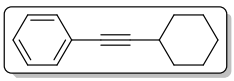
**1-(Cyclohexylethynyl)-4-methylbenzene (Table 2.3, entry 11):** Yellow liquid, **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.29-7.27 (m, 2H), 7.13-7.10 (m, 2H), 2.57 (d, 1H, *J* = 8.7 Hz), 2.31 (s, 3H), 1.73-1.26 (m, 10H) ppm.**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 137.4, 131.8, 131.5, 129.1, 129.0, 121.1, 93.7, 80.6, 40.5, 32.8, 29.7, 26.0, 21.5 ppm.



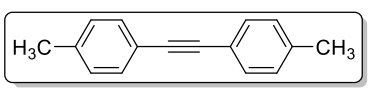
**1-(Dodec-1-yn-1-yl)-benzene (Table 2.3, entry 12):** Yellow liquid, **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.37 (m, 2H), 7.27-7.25 (m, 3H), 2.39 (t, 2H, *J* = 6.8 Hz), 1.62-1.27 (m, 12H), 0.88 (t, 3H, *J* = 6.8 Hz) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 131.6, 128.2, 127.5, 124.1, 90.5, 80.6, 31.9, 29.7, 29.4, 29.2, 28.8, 22.7, 19.4, 14.2 ppm.



**1-(Hex-1-yn-1-yl)-benzene (Table 2.3, entry 13)**: Yellow liquid; **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.38 (m, 2H), 7.27-7.25 (m, 3H), 2.41 (t, 2H, *J* = 6.8 Hz), 1.59-1.47 (m, 4H), 0.94 (t, 3H, *J* = 7.3 Hz) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 131.6, 128.2, 127.5, 124.1, 90.5, 80.6, 29.7, 22.1, 19.1, 13.7 ppm.

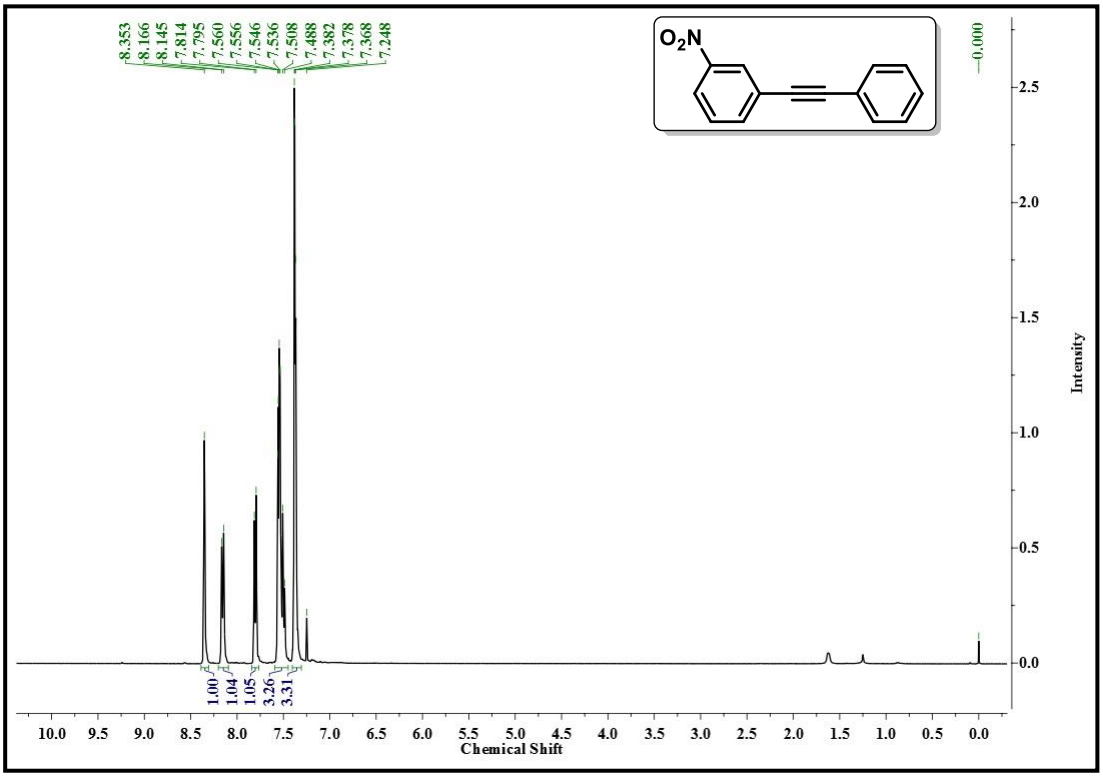


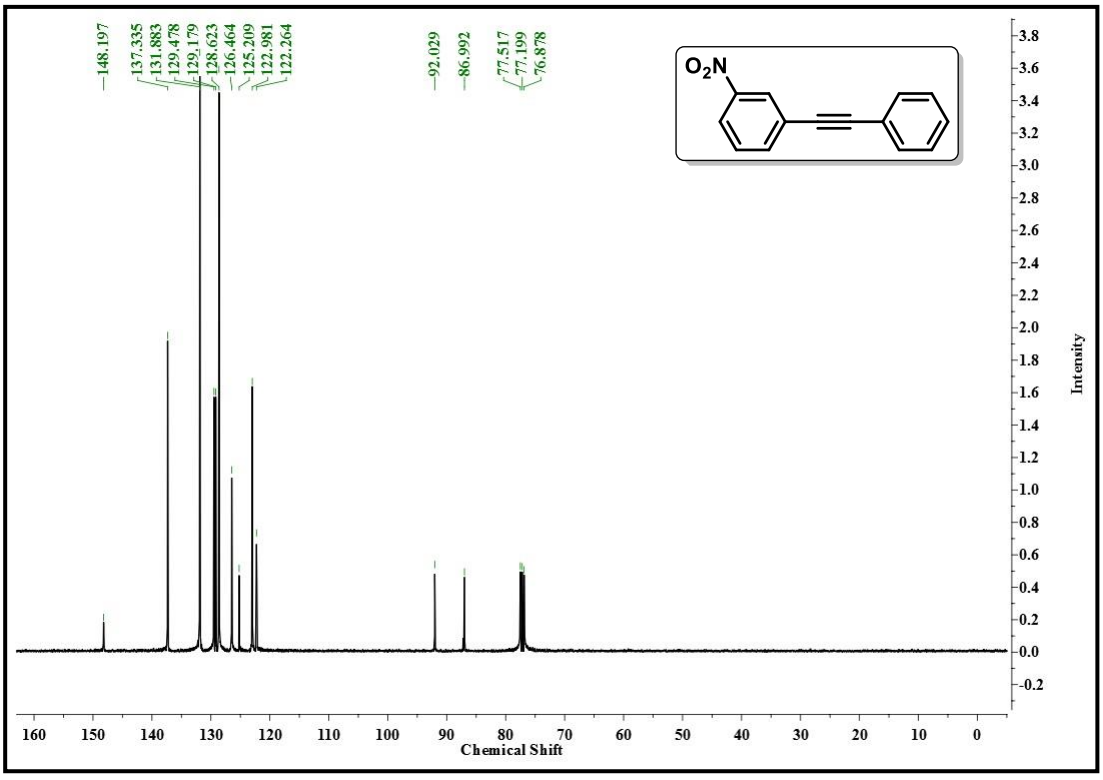
**1-(Cyclohexylethynyl)benzene (Table 2.3, entry 14):** Yellow liquid, **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.38 (m, 2H), 7.29-7.25 (m, 3H), 2.59-2.57 (m, 1H), 1.89-1.34 (m, 10H) ppm.**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 131.9, 131.6, 128.3, 128.2, 127.4, 94.5, 80.5, 32.7, 26.0, 23.4, 22.8 ppm.



**1-Methyl-4-[2-(*p*-tolyl)ethynyl]benzene** (**Table 2.3 entry 16):** White solid, m.p. 126-128 °C, **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.39 (m, 4H), 7.14-7.12 (d, 4H, *J* = 8.2 Hz), 2.35 (s, 6H) ppm. **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 138.2, 131.5, 129.3, 120.4, 88.9, 87.2, 21.5 ppm.

## $^{1}H$ and $^{13}C$ NMR spectra of 1-Nitro-3-(2-phenylethynyl)benzene



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