Pd(II)/Mg-La mixed oxide catalyst for cyanation of aryl C–H bonds

4.1. Introduction

 Aryl nitriles are valuable intermediates in synthetic organic chemistry since the nitrile group is an important precursor for a broad range of functional group transformations leading to the formation of amines, aldehydes, acids, ketones, amides and heterocycles [1]. Aryl nitriles are also key motifs in pharmaceuticals, agrochemicals, dyes and natural products [2].

 The Classical methods for the synthesis of nitrile containing compounds requires prefunctionalization of the arenes with aryl iodides/bromides (Rosenmund-von Braun reaction) [3] and aryl diazonium compounds (Sandmeyer reaction) [4]. Other precursors such as aldehydes (Schmidt reaction), aldoximes (by dehydration) or primary carboxyamides are also used in the cyanation reactions. Industrially, ammoxidation reaction is used to synthesise ary nitriles from toluene derivatives in the presence of oxygen and ammonia using heterogeneous catalysts at high temperature (around 500 °C) and high pressure. However, these approaches suffer from multiple synthetic steps, high cost, harsh reaction conditions, limited functional group tolerance, and use of toxic cyano sources.

4.2 State-of-the-art

 Hence, efforts have been devoted towards the catalytic routes to synthesise aryl nitriles via transition metal catalyzed cyanation of haloarenes using the metal bound precursor MCN (M = Cu, Na, K, Zn), TMSCN or K₄Fe(CN)₆ as the source of “CN” unit [5-10]. Transitional metal catalyzed C-H bond functionalization reactions have now emerged as one of the most efficient tools in the formation of C-C and C-hetero atoms bonds[11]. However, direct cyanation of aryl C-H bonds is comparatively underdeveloped compared to other types of C-H functionalization reactions. The first example of Cu-mediated direct C-H bond cyanation was reported by Yu’s group in 2006. They used 2-arylpyridine as a substrate and TMSCN or CH₃NO₂ as the “CN” source [12] (Scheme 4.1).

![Scheme 4.1](image_url)
Other cyanide sources such as metal cyanides [13], NCTS [14], TsCN [15], Me$_3$SiN$_3$ [16], BrCN [17] and acetone cyanohydrine [18] could be used in the transition metal catalyzed oxidative cyanation through C-H bond activation. In pursuit of greener and safer “CN” sources for the cyanation reaction, recently, Chang and his co-workers reported an elegant and effective cyanation process through Pd catalyzed direct C-H bond functionalization using a combination of DMF and ammonia [19] (Scheme 4.2a) or ammonium iodide [20] (Scheme 4.2b) as a “CN” source.

**Scheme 4.2a** DMF and ammonia as combined cyanide source

\[
\text{(2-Py)} + \text{NH}_3(\text{aq}) \xrightarrow{\text{Pd(OAc)}_2 (10 \text{ mol}%), \text{CuBr (1.1 equiv.)}} \text{(2-Py)}\text{CN}
\]

DMF, O$_2$, 130°C, 18 h

**Scheme 4.2b** DMF and NH$_4$I as combined cyanide source

Very recently, Jiao et al. reported the novel cyanation of heterocycles by using DMF both as the cyanating source and solvent [21]. Cheng et al. pioneered the combined use of NH$_4$HCO$_3$ and DMSO as the source of cyanide in the Pd-catalyzed direct cyanation of indoles [22] (Scheme 4.3).

**Scheme 4.3** Safe cyanation of indoles
These cyanating processes obviate the need to prefunctionalize the arenes and also they use non-toxic single or combined “CN” sources. However, despite their exceptional performance, there are several challenges that have prevented the widespread practical application of transitional metal catalyzed oxidative cyanation process through C–H bond activation. One such challenge arises due to the inability to recover and reuse the expensive transitional metals. Industry favors catalytic processes induced by a heterogeneous catalyst over the homogeneous one in view of its ease of handling, simple workup, and regenerability. Recently, Figueras and co-workers examined the direct condensation of alcohols [23] and Michael addition reactions [24] over highly basic Mg-La mixed oxide catalyst. Earlier, the catalytic activity of the Mg-La mixed oxide was demonstrated in the condensation of aldehydes and imines with ethyl diazoacetate using water as a solvent [25]. Figueras and co-workers reported an air- and moisture-stable palladium impregnated on Mg-La mixed oxide catalyst (Pd/Mg-La) as an efficient heterogeneous catalyst in the Heck and the Suzuki–Miyaura reactions [26].

4.3 Present work

In this investigation, the activity of this Pd(II)/Mg-La mixed oxide catalyst was explored towards the cyanation of aromatic C–H bonds by using the combination of NH$_4$HCO$_3$ and DMSO as the “CN” source to provide aromatic nitriles (Scheme 4.4).

![Scheme 4.4 Pd/Mg-La mixed oxide catalyzed cyanation of aryl C–H bonds](image-url)

4.4 Results and discussion

4.4.1 X-Ray diffraction

The Mg-La mixed oxide was synthesized by co-precipitation of Mg and La nitrates and the Pd-doped Mg-La mixed oxide catalyst was prepared by impregnation method to obtain Pd(II)/Mg-La mixed oxide. The X-ray diffraction patterns of the fresh and used Pd(II)/Mg-La catalysts revealed the presence of both La$_2$O$_2$(CO$_3$) and PdO
Chapter 4  Pd/Mg-La Mixed Oxide Catalyst for Cyanation of Aryl C–H Bonds

phases (Figure 4.1). Diffraction lines appeared at $2\theta = 29.55^\circ$, $22.84^\circ$, $13.1^\circ$ [ICDD # 23-0435] and their corresponding ‘d’ values 0.302, 0.389 and 0.675 nm are attributed to lanthanum oxide carbonate phase. The diffraction peaks are observed due to PdO phase at $2\theta = 31.7^\circ$, $45.54^\circ$, $27.33^\circ$ with the corresponding ‘d’ values of 0.282, 0.199, 0.326 nm that are in good agreement with ICDD # 46-1211.

![XRD patterns of the Pd(II)/Mg-La mixed oxide: fresh and used catalysts](image)

Figure 4.1 XRD patterns of the Pd(II)/Mg-La mixed oxide: fresh and used catalysts

4.4.2 Transmission electron microscopic analysis

The transmission electron microscope (TEM) images of fresh and used (after 1st cycle) Pd(II)/Mg-La catalysts are reported in Figure 4.2a and Figure 4.2b.

![TEM images of the Pd(II)/Mg-La mixed oxide: [a] fresh and [b] used catalyst (recovered after 1st cycle)](image)

Figure 4.2. TEM images of the Pd(II)/Mg-La mixed oxide: [a] fresh and [b] used catalyst (recovered after 1st cycle).
The average Pd particle size is measured from TEM images (Figure 4.2) and found to be 25 and 33 nm for fresh and used catalysts respectively. The shapes of palladium particles are spherical in both the fresh and used samples.

### 4.4.3 X-ray photoelectron spectroscopy

The XPS analysis of the fresh and used (after 4th cycle) Pd(II)/Mg-La mixed oxide catalyst is presented in **Figure 4.3**. The PdO species are present on the surface which was confirmed by XPS signal appeared at binding energies 336 eV and 341.2 eV of Pd 3d\(_{5/2}\) and Pd 3d\(_{3/2}\) respectively over fresh catalyst and 336.2 eV and 341.8 eV of 3d\(_{5/2}\) and 3d\(_{3/2}\) over used catalyst.

![XPS spectra](image)

**Figure 4.3** The XPS spectra of (Pd 3d\(_{5/2}\), 3d\(_{3/2}\)) [a] fresh and [b] used Pd(II)/Mg-La mixed oxide catalysts.

### 4.4.4 Catalytic activity of Pd(II)/Mg-La mixed oxide catalyzed cyanation of aryl C–H bonds

The optimization of the reaction conditions was performed by using 2-phenylpyridine as the model substrate. When 5.6 mol% of Pd(II)/Mg-La catalyst, 1 equiv of Cu(OAc)\(_2\) and a combination of NH\(_4\)HCO\(_3\) (1 equiv) and DMSO (2 mL) as the cyanating agent were used, the desired product 2-(pyridin-2-yl)benzonitrile was obtained in 43% yield (Table 4.1, entry 1). Encouraged by these results, several optimization studies were conducted by altering the catalyst, oxidant, nitrogen source and solvents. Results from these studies are summarized in Table 4.1. An improvement in the product yield was observed when the amount of Cu(OAc)\(_2\) and NH\(_4\)HCO\(_3\) was increased from 1
equivalent to 2 and 2.1 equivalents respectively (Table 4.1, entries 1-3). As seen in Table 4.1, the choice of oxidant has a crucial role in the reaction outcome. Excellent yield of the product was obtained when the oxidant was either Cu(NO$_3$)$_2$ or Cu(OAc)$_2$ (Table 4.1, entries 1-4); whereas reaction failed with K$_2$S$_2$O$_8$ and aqueous TBHP (Table 4.1, entries 5 & 6). Interestingly, changing the solvent from DMSO to DMF had a detrimental effect on the yield of the product as only 58% yield was obtained (Table 4.1, entry 8). Remarkably, NH$_4$HCO$_3$ was found to be the better source of nitrogen in the cyanation reaction as only 20% product yield was obtained using ammonia as a nitrogen source (Table 4.1, entry 7). The use of other heterogeneous palladium catalysts developed in our lab such as Pd(II)/MgO and Pd(II)/La$_2$O$_3$ gave inferior yield of the product than using Pd(II)/Mg-La mixed oxide catalyst (Table 1, entries 9 & 10). It is important to note that the presence of both palladium and copper is necessary for the formation of the product (Table 4.1, entries 11 & 12).

Table 4.1. Screening of reaction parameters.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant/equiv.</th>
<th>N source/equiv.</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(II)/Mg-La</td>
<td>Cu(OAc)$_2$/1</td>
<td>NH$_4$HCO$_3$/1</td>
<td>DMSO</td>
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</tr>
<tr>
<td>2</td>
<td>Pd(II)/Mg-La</td>
<td>Cu(OAc)$_2$/2</td>
<td>NH$_4$HCO$_3$/1</td>
<td>DMSO</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>Pd(II)/Mg-La</td>
<td>Cu(OAc)$_2$/2</td>
<td>NH$_4$HCO$_3$/2.1</td>
<td>DMSO</td>
<td>92</td>
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<tr>
<td>4</td>
<td>Pd(II)/Mg-La</td>
<td>Cu(NO$_3$)$_2$/2</td>
<td>NH$_4$HCO$_3$/2.1</td>
<td>DMSO</td>
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</tr>
<tr>
<td>5</td>
<td>Pd(II)/Mg-La</td>
<td>K$_2$S$_2$O$_8$/2</td>
<td>NH$_4$HCO$_3$/2.1</td>
<td>DMSO</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Pd(II)/Mg-La</td>
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<td>Pd(II)/Mg-La</td>
<td>Cu(NO$_3$)$_2$/2</td>
<td>NH$_3$(25% aq)/2.1</td>
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<td>NH$_4$HCO$_3$/2.1</td>
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<td>DMSO</td>
<td>58</td>
</tr>
<tr>
<td>11</td>
<td>Pd(II)/Mg-La</td>
<td>-</td>
<td>NH$_4$HCO$_3$/2.1</td>
<td>DMSO</td>
<td>0</td>
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<td>12</td>
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<td>Cu(NO$_3$)$_2$/2</td>
<td>NH$_4$HCO$_3$/2.1</td>
<td>DMSO</td>
<td>0</td>
</tr>
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</table>

$^a$Reaction conditions: 30 mg Pd catalyst (5.6 mol% of Pd), 2-Phenylpyridine (0.5mmol), oxidant (2 equiv), N source (2.1 equiv), solvent (2 mL), 140 °C, 18h
4.4.5 Substrate scope

Eventually, the catalytic system consisting of Pd(II)/Mg-La (30 mg, 5.6 mol% of Pd), Cu(NO$_3$)$_2$ (2 equiv.) as the oxidant and the combination of NH$_4$HCO$_3$ (2.1 equiv.) and DMSO as the cyanating reagent at 140 °C temperature were chosen for the cyanation reaction of an array of 2-phenylpyridine derivatives and the results are summarized in Figure 4. With 4-methyl 2-phenylpyridine, the corresponding mono cyano derivative was obtained in 82% yield (Table 4.2, entry 2). To some extent, the reaction was sensitive to methyl substitution on the meta position of the 2-phenyl ring (Table 4.2, entry 3), delivering the product in lower yield than its para counterpart (Table 4.2, entries 2 and 3). In contrast, for an electron deficient 4-fluoro, -chloro and –bromo substituted analogues, moderate yields of the products were obtained (Table 4.2, entries 4, 5 and 6). Other functional groups such as –CF$_3$, -CN and -OMe also survived the reaction conditions, giving the corresponding cyano derivatives of 2-phenylpyridine in moderate yields (Table 4.2, entries 7, 9 and 10). Interestingly, bulkier 2-naphthyl and 1-naphthyl derivatives of pyridine also furnished the cyanation product with moderate yields under the present reaction conditions (Table 4.2, entries 11 & 12). Isoquinoline and quinoline could act as a directing group as well, delivering the corresponding aryl nitriles in 79% and 73% yields respectively (Table 4.2, entries 13 and 14). In addition, benzo[h]quinoline also demonstrated high efficiency in the current cyanation reaction (Table 4.2, entry 14).

Table 4.2 Substrate scope of cyanation of aryl C–H bonds
**Chapter 4  Pd/Mg-La Mixed Oxide Catalyst for Cyanation of Aryl C–H Bonds**

![Reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield(%)</th>
</tr>
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<td><img src="image18" alt="Product" /></td>
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<td><img src="image22" alt="Product" /></td>
<td>53</td>
</tr>
<tr>
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<td><img src="image23" alt="Substrate" /></td>
<td><img src="image24" alt="Product" /></td>
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<tr>
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<td><img src="image29" alt="Substrate" /></td>
<td><img src="image30" alt="Product" /></td>
<td>63</td>
</tr>
</tbody>
</table>

*Reaction conditions: 30 mg Pd(II)/Mg-La (5.6 mol% of Pd), Substrate (0.5mmol), Cu(NO₃)₂ (2 equiv), NH₄HCO₃ (2.1 equiv), DMSO (2 mL), 140 °C, 18h*
4.4.6 Recyclability

The feasibility of repeated use of Pd(II)/Mg-La mixed oxide catalyst in the cyanation reaction was also examined. In Figure 4.4, the results from the investigation of recycling of the catalyst were presented using 2-phenylpyridine as the model substrate on 1.5 mmol scale, 90 mg Pd(II)/Mg-La catalyst (5.6 mol% of Pd), Cu(NO₃)₂ (2 equiv), NH₄HCO₃ (2.1 equiv) and DMSO (6 mL) at 140 °C for 18 h. The Pd(II)/Mg-La mixed oxide catalyst shows consistent activity and selectivity up to 4 cycles. After each cycle, Pd(II)/Mg-La mixed oxide catalyst was recovered by simple centrifugation, washed, air-dried and used directly for the next cycle without further purification. No loss of catalytic activity was observed for the catalyst in the cyanation of aryl C–H Bonds. Moreover, leaching studies of the metal after the first cycle was determined by AAS and was found to be negligible.

![Figure 4.4 Recyclability of the catalyst. 90 mg Pd Catalyst (5.6 mol% of Pd), 2-Phenylpyridine (1.5mmol), Oxidant (2 equiv), N source (2.1 equiv), Solvent (6 mL), 140 °C, 18h](image)

4.5 Plausible mechanism

In scheme 4.5, a plausible mechanism for the cyanation of 2-phenylpyridine is depicted. In the initial step, it is assumed that a palladated intermediate A is generated through the C–H bond activation. In the next step, ligand exchange of CN⁻ generates the intermediate Pd(II) species B. The formation of CN⁻ occurred in the presence of Cu(OAc)₂, DMSO and NH₃ which was formed through the decomposition of NH₄HCO₃.
Finally, the intermediate B undergoes reductive elimination to produce the product and Pd(0) species, which re-oxidises to Pd(II) in the presence of Cu(II).

Scheme 4.5  Plausible reaction mechanism of Pd/Mg-La mixed oxide catalyzed cyanation of aryl C–H bonds

4.6 Conclusions

- A simple and efficient method for the cyanation of aromatic C-H bonds by using palladium/magnesium-lanthanum mixed oxide
- A green protocol for the generation of a cyano unit from two readily available precursors (NH$_4$HCO$_3$ and DMSO) has been demonstrated.
- The reaction represents a convenient and safe method for the cyanation of the 2-arylpyridine derivatives.
- The catalyst can be readily recovered and reused. This methodology may find widespread use in organic synthesis.

4.7 Experimental

4.7.1 Preparation of Pd(II)/Mg-La mixed oxide

The Mg-La mixed oxide was obtained by co-precipitation of Mg and La nitrates (0.39 mol and 0.13 mol, in water 0.5 L for an atomic ratio Mg/La = 3) at a constant pH = 10.0 using a mixture of KOH (1 mol) and K$_2$CO$_3$ (0.26 mol) in 0.52 L of distilled water.
The gel was washed until the pH reached neutral followed by oven dried at 120 °C for 16 h subsequently calcined in static air at 750 °C/5 h at a ramping rate of 10 °C/min. The Pd supported on Mg-La mixed oxide catalyst was prepared by impregnation method. In a typical method, Mg-La mixed oxide (1.5 g) was suspended in 150 mL of aqueous palladium (II) nitrate hydrate (Pd(NO$_3$)$_2$.xH$_2$O ) [0.345 g, 1.5 mmol] solution and stirred at 25 °C for 12 h under a nitrogen atmosphere. The solid was filtered, washed with distilled water, dried at 100 °C and calcined at 350 °C for 5h.

4.7.2 Preparation of substrates

Substrates a, b and n are commercially available and purchased from Sigma Aldrich. Other substrates (c, d, e, f, g, h, i, j, k, l, m, and o) were prepared by using Pd(II)/Mg-La mixed oxide catalyst via Suzuki coupling (Scheme 4.6). A mixture of aryl bromide (4 mmol), arylboronic acid (6 mmol), Pd(II)/Mg-La (50 mg), K$_3$PO$_4$.7H$_2$O (8 mmol), 50% aqueous isopropanol (20 mL) was stirred at 80 °C in air for the indicated time. The mixture was added to brine and extracted four times with diethyl ether. The solvent was concentrated under vacuum and the product was isolated by short chromatography on a silica gel column$^{[2]}$.
Scheme 4.6 Reaction scheme for preparation of starting compounds

4.7.3 General catalytic procedure

A 10 mL round bottom flask was charged with 2-phenylpyridine (0.5 mmol), NH₄HCO₃ (1.05 mmol, 2.1 equiv.), Pd(II)/Mg-La (30 mg, 5.6 mol%), Cu(NO₃)₂ (1 mmol, 2 equiv.) and DMSO (2 mL). The round bottom flask was kept stirring at 140 °C for 18 h. After the completion of the reaction, as monitored by TLC, the catalyst was separated by simple centrifugation and used for next cycle. The reaction mixture was washed with brine (10 mL) and then extracted with ethyl acetate (3×5 mL). The ethyl acetate extract was purified by flash column chromatography on silica gel to give the product.

Spectroscopic characterization of some of the representative compounds

2-(Pyridin-2-yl)benzonitrile (Table 4.2, entry 1)

\[
{^1}H \text{ NMR (500 MHz, CDCl}_3) \ \delta \ 8.78-8.77 \ (m, \ 1H), \ 7.86-7.77 \ (m, \ 4H), \ 7.69 \ (td, \ J = 7.6, 1.3 \ Hz, \ 1H), \ 7.50 \ (td, \ J = 7.6, 1.2 \ Hz, \ 1H), \ 7.37-7.35 \ (m, \ 1H) \ (\text{Figure 4.4}); \ {^{13}}C \text{ NMR (75 MHz, CDCl}_3) \ \delta \ 155.1, \ 149.8, \ 143.4, \ 136.8, \ 134.0, \ 132.7, \ 129.9, \ 128.7, \ 123.3, \ 123.2, \ 118.6, \ 111.0 \ (\text{Figure 4.5}); \ MS \ (ESI) \ 181 \ (M+H).
\]

5-Methyl-2-(pyridin-2-yl)benzonitrile (Table 4.2, entry 2)

\[
{^1}H \text{ NMR (400 MHz, CDCl}_3) \ \delta \ 8.76-8.75 \ (m, \ 1H), \ 7.8 \ (td, \ J = 7.9, 1.6 \ Hz, \ 1H), \ 7.77-7.73(m, \ 2H), \ 7.60 \ (d, \ J = 1.0 \ Hz, \ 1H), \ 7.49 \ (dd, \ J = 8.0, 1.0 \ Hz, \ 1H), \ 7.34-7.32 \ (m, \ 1H), \ 2.44 \ (s, \ 3H) \ (\text{Figure 4.6}); \ {^{13}}C \text{ NMR (75 MHz, CDCl}_3) \ \delta \ 155.2, \ 149.8, \ 140.7, \ 139.0,
\]
136.7, 134.4, 133.7, 129.8, 123.0, 122.6, 118.8, 110.7, 20.8 (Figure 4.7); MS (ESI) 195 (M+H).

4-Methyl-2-(pyridin-2-yl)benzonitrile (Table 4.2, entry 3)

![4-Methyl-2-(pyridin-2-yl)benzonitrile](image)

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.77-8.76 (m, 1H), 7.78-7.77 (m, 2H), 7.68-7.66 (m, 2H), 7.38-7.30 (m, 2H), 2.47 (s, 3H) (Figure 4.8); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.3, 149.8, 143.8, 143.2, 136.7, 133.9, 130.6, 129.4, 123.2, 123.1, 118.9, 107.9, 21.7 (Figure 4.9); MS (ESI) 195 (M+H).

5-Fluoro-2-(pyridin-2-yl)benzonitrile (Table 4.2, entry 4)

![5-Fluoro-2-(pyridin-2-yl)benzonitrile](image)

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.77-8.66 (m, 1H), 7.87-7.83 (m, 2H), 7.77-7.75 (m, 1H), 7.50 (dd, $J = 8.0, 2.7$ Hz, 1H), 7.43-7.35 (m, 2H) (Figure 4.10); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 161.9 (d, $J_{C-F} = 252.4$ Hz), 154.2, 149.9, 139.8 (d, $J_{C-F} = 3.6$ Hz), 136.9, 132.1 (d, $J_{C-F} = 8.1$ Hz), 123.3, 123.0, 120.6 (d, $J_{C-F} = 25.4$ Hz), 120.4, 117.4 (d, $J_{C-F} = 2.7$ Hz), 112.3 (d, $J_{C-F} = 9.0$ Hz) (Figure 4.11); MS (ESI) 199 (M+H).

5-Chloro-2-(pyridin-2-yl)benzonitrile (Table 4.2, entry 5)

![5-Chloro-2-(pyridin-2-yl)benzonitrile](image)

$^1$H NMR (CDCl$_3$, 500 MHz) δ 8.78-8.71 (m, 1H), 7.86-7.77 (m, 4H), 7.66 (dd, $J = 8.3, 2.1$Hz, 1H), 7.39-7.36 (m, 1H) (Figure 4.12); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 154.0, 150.0, 141.7, 136.9, 134.9, 133.5, 133.1, 131.2, 123.5, 123.0, 117.4, 112.3 (Figure 4.13).

5-Bromo-2-(pyridin-2-yl)benzonitrile (Table 4.2, entry 6)
$^1$H NMR (CDCl$_3$, 300 MHz) δ 8.77 (d, $J = 4.3$ Hz, 1H), 7.93 (d, $J = 1.7$ Hz, 1H), 7.87-7.73 (m, 4H), 7.40-7.35 (m, 1H) (Figure 4.14); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 154.0, 150.0, 142.1, 136.9, 136.4, 136.0, 131.3, 123.5, 123.0, 122.5, 117.2, 112.6 (Figure 4.15); MS (ESI) 260 (M+H).

2-(Pyridin-2-yl)-4-(trifluoromethyl)benzonitrile (Table 4.2, entry 7)

$^1$H NMR (CDCl$_3$, 500 MHz) δ: 8.80 (d, $J = 4.7$ Hz, 1H), 8.05 (s, 1H), 8.01 (d, $J = 8.2$ Hz, 1H), 7.95 (d, $J = 8.3$ Hz, 1H), 7.90 (t, $J = 7.7$ Hz, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.47–7.40 (m, 1H) (Figure 4.16); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.6, 150.1, 146.4, 137.0, 131.8 (q, $J_{C-F} = 29.9$ Hz), 130.9 (q, $J_{C-F} = 3.6$ Hz), 130.6, 129.3 (q, $J_{C-F} = 3.6$ Hz), 124.0, 123.2, 122.8 (q, $J_{C-F} = 272$ Hz), 117.4, 112.0 (Figure 4.17); MS (ESI) 249 (M+H).

5-Phenyl-2-(pyridin-2-yl)benzonitrile (Table 4.2, entry 8)

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.80-8.79 (m, 1H), 8.10 (d, $J = 1.8$ Hz, 1H), 7.94-7.89 (m, 2H), 7.87-7.83 (m, 2H), 7.63-7.61 (m, 2H), 7.51-7.48 (m, 2H), 7.45-7.41 (m, 1H), 7.38-7.35 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 154.8, 149.9, 141.8, 141.8, 138.2, 136.8, 132.5, 131.3, 130.4, 129.1, 128.4, 126.9, 123.2, 123.1, 118.7, 111.3; MS (ESI) 257 (M+H).
4-(pyridin-2-yl)isophthalonitrile (Table 4.2, entry 9)

![Structure image]

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$: 8.82-8.81 (m, 1H), 8.09 (d, $J = 1.5$ Hz, 1H), 8.03 (d, $J = 8.2$ Hz, 1H), 7.96 (dd, $J = 1.6$, 8.2 Hz, 1H), 7.90 (td, $J = 1.6$, 7.2 Hz, 1H), 7.86-7.84 (m, 1H), 7.46-7.43 (m, 1H). $^{13}$CNMR (CDCl$_3$, 125 MHz) $\delta$: 153.1, 150.2, 146.9, 137.3, 137.1, 135.7, 130.9, 124.3, 123.3, 116.6, 116.5, 113.2, 112.4; MS (ESI) 206 (M+H).

5-methoxy-2-(pyridin-2-yl)benzonitrile (Table 4.2, entry 10)

![Structure image]

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.74 (d, $J = 4.5$ Hz, 1H), 7.84-7.73 (m, 3H), 7.33-7.29 (m, 1H), 7.27 (d, $J = 2.6$ Hz, 1H), 7.22 (dd, $J = 2.6$, 8.6 Hz, 1H), 3.89 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 159.4, 154.9, 149.7, 136.7, 135.9, 131.2, 122.7, 122.6, 119.3, 118.6, 118.4, 111.6, 55.6; MS (ESI) 211 (M+1).

3-(pyridin-2-yl)naphthalene-2-carbonitrile (Table 4.2, entry 11)

![Structure image]

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.82-8.81 (m, 1H), 8.40 (s, 1H), 8.28 (s, 1H), 7.95-7.34 (m, 2H), 7.87-7.86 (m, 2H), 7.66-7.61 (m, 2H), 7.39-7.46 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 155.4, 149.8, 143.6, 136.7, 134.4, 132.9, 132.4, 131.7, 129.6, 128.8, 127.9, 127.7, 118.9, 108.6; MS (ESI) 231 (M+1).
1-(Pyridin-2-yl)-2-naphthonitrile (Table 4.2, entry 12)

![Chemical structure of 1-(Pyridin-2-yl)-2-naphthonitrile]

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.87 (d, $J$ = 4.3, Hz, 1H), 7.99-7.90 (m, 3H), 7.74-7.70 (m, 2H), 7.66-7.60 (m, 2H), 7.56-7.53 (m, 1H), 7.50-7.45 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.2, 149.9, 144.4, 136.7, 135.0, 131.1, 129.4, 128.7, 128.3, 127.9, 126.8, 126.7, 125.6, 123.5, 118.5, 109.7; MS (ESI) 231 (M+H).

2-(Isoquinolin-1-yl)benzonitrile (Table 4.2, entry 13)

![Chemical structure of 2-(Isoquinolin-1-yl)benzonitrile]

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.66 (d, $J$ = 5.6 Hz, 1H), 7.95-7.93 (m, 1H), 7.88 (dd, $J$ = 7.7, 0.7 Hz, 1H), 7.78-7.72 (m, 4H), 7.67-7.66 (m, 1H), 7.63-7.55 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.8, 142.8, 142.0, 136.6, 133.3, 132.2, 130.8, 130.4, 128.8, 127.7, 127.1, 126.7, 126.4, 121.3, 117.5, 113.0; MS (ESI) 231 (M+H).

2-(quinolin-2-yl)benzonitrile (Table 4.2, entry 14)

![Chemical structure of 2-(quinolin-2-yl)benzonitrile]

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.32 (d, $J$ = 8.5 Hz, 1H), 8.22 (d, $J$ = 8.5 Hz, 1H), 7.96 (d, $J$ = 7.9 Hz, 1H), 7.89-7.84 (m, 3H), 7.79-7.72 (m, 2H), 7.62-7.59 (m, 1H), 7.56-7.53 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.1, 148.0, 143.6, 137.0, 134.2, 132.8, 130.1, 129.7, 189.9, 128.9, 127.5, 127.3, 127.2, 120.5, 118.6, 111.5; MS (ESI) 231 (M+H).
Benzo[h]quinoline-10-carbonitrile (Table 4.2, entry 14)

![Chemical structure of 2-(Pyridin-2-yl)benzonitrile](image)

**1H NMR (CDCl₃, 500 MHz)** δ: 9.14 (dd, J = 4.4, 1.8 Hz, 1H), 8.23 (dd, J = 8.0, 1.6 Hz, 1H), 8.17-8.12 (m, 2H), 7.82 (q, J = 8.8 Hz, 2H), 7.74 (t, J = 7.6 Hz, 1H), 7.63 (dd, J = 8.0, 4.4 Hz, 1H). **13C NMR (CDCl₃, 125 MHz)** δ: 148.4, 144.4, 136.2, 135.6, 134.0, 132.6, 130.7, 127.3, 127.2, 127.0, 126.9, 123.0, 120.7, 108.9.

**1H and 13C NMR spectra some important products**

**Figure 4.4:** **1H Spectrum of 2-(Pyridin-2-yl)benzonitrile**
Figure 4.5: $^{13}$C NMR Spectrum of 2-(Pyridin-2-yl)benzonitrile

Figure 4.6: $^1$H Spectra of 5-Methyl-2-(pyridin-2-yl)benzonitrile
Figure 4.7: $^{13}$C Spectrum of 5-Methyl-2-(pyridin-2-yl)benzonitrile

Figure 4.8: $^1$H NMR Spectrum of 4-Methyl-2-(pyridin-2-yl)benzonitrile
Figure 4.9: $^{13}$C NMR Spectra of 4-Methyl-2-(pyridin-2-yl)benzonitrile

Figure 4.10: $^1$H NMR Spectrum of 5-Fluoro-2-(pyridin-2-yl)benzonitrile
Figure 4.11: $^{13}$C NMR Spectrum of 5-Fluoro-2-(pyridin-2-yl)benzonitrile

Figure 4.12: $^1$H NMR Spectrum of 5-Chloro-2-(pyridin-2-yl)benzonitrile
Figure 4.13: $^{13}$C NMR Spectrum of 5-Chloro-2-(pyridin-2-yl)benzonitrile

Figure 4.14: $^1$H NMR Spectrum of 5-Bromo-2-(pyridin-2-yl)benzonitrile
Figure 4.15: $^{13}$C NMR Spectrum of 5-Bromo-2-(pyridin-2-yl)benzonitrile

Figure 4.16: $^1$H NMR Spectra of 2-(Pyridin-2-yl)-4-(trifluoromethyl)benzonitrile
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Figure 4.17: $^{13}$C NMR Spectra of 2-(Pyridin-2-yl)-4-(trifluoromethyl)benzonitrile

4.8 References


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