CHAPTER 5

Reactions of β-Chloroenones with Cyanomethylene Compounds: Synthesis of 2-Pyridones and 2-Hydroxypyridines

5.1. Introduction

Heterocycles are among the most important structural classes of chemical substances and are particularly well-represented among natural products and pharmaceuticals. One striking structural feature inherent to heterocycles, which continues to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in a defined three-dimensional representation, thereby allowing for far less degrees of conformational freedom than the corresponding conceivable acyclic structures. In addition, as a result of the presence of heteroatoms such as O, N, and S, heterocycles often exhibit altered absorption, distribution, metabolism, and excretion properties. Among them pyridine and its derivatives are pharmacologically important molecules. They are extensively used in medicines as drugs for the treatment of various diseases.¹ They also find applications as agrochemicals and anticancer agents.² Extensive studies have been carried out on the synthesis of these valuable compounds owing to their importance as drugs and biologically active natural products.³ A recent pharmacological evaluation revealed the importance of various functionalized 2-pyridones as cardiotonic agents similar to milrinone which is the most effective nonglycosidic cardiotonic agent clinically used for the treatment of severe heart failure.⁴ An important analogue of milrinone, 5-aroyl-2-oxo-3-pyridinecarbonitrile was synthesized in our laboratory from aroylformylketene dithioacetal following a two step reaction strategy involving the condensation of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes with malononitrile followed by cyclization with conc. HCl or Br₂ or reaction of aroylformylketene dithioacetal
with ethylcyanoacetamide in the presence of ammonium acetate and acetic acid. Further, β-chloroenones, being another valuable 1,3-bielectrophile, were investigated for their reactions with cyanomethylene compounds, which is the subject matter of the present Chapter.

\[
\begin{align*}
\text{Milrinone} \\
\end{align*}
\]

5.2. General Methods of synthesis of pyridones and its derivatives

2-Pyr-dones are generally prepared from N-substituted pyridinium salts which are obtained from functionalized pyridines by alkylation or oxidation. Extensive use of this methodology has been made for the synthesis of biologically active aroylpyridones and naturally occurring alkaloids. One of the general methods for the synthesis of 2-pyridone derivatives involve cross condensation of cyanoacetamides with β-dicarbonyl compounds accompanied by cyclization yielding 2-pyridones. For example the reaction of substituted acetylacetones 1 with cyanoacetamides resulted in the formation of 4,5,6-trisubstituted-2-oxo-1, 2-dihydro-3-pyridinecarbonitriles 3 (Scheme 1).  

\[
\begin{align*}
\text{Scheme 1} \\
\end{align*}
\]

Recently N-substituted cyanoacetamides were treated with 1,3-dicarbonyl compounds 4 under microwave irradiation to prepare 2-hydroxypyr-dine derivatives 6 (Scheme 2).
Regioselective synthesis of bicyclic 3-cyanopyridin-2(1H)-ones 8 have been carried out by using cyclic 1,3-diketones 7 as substrates with cyanoacetamides 2 (Scheme 3). 

Unsymmetrical 1,3-carbonyl compounds 9 when condensed with cyanoacetamide 2 led to the formation of two isomeric products 10 and 11 (Scheme 4).

Reactions of 1,3-diketones 4 with ethyl cyanoacetate or malononitrile afforded 4,6-disubstituted-2-oxopyridine-3-carboxylates or nicotinonitrile derivative 12 (Scheme 5).
Versatile synthetic intermediates such as enaminones along with alkyl cyanoesters are used for the synthesis of 2-pyridone derivatives. Synthesis of 1,2-dihydro-2-oxo-3-pyridinecarbonitriles 15 have been carried out recently by Mosti et al from enaminoketones 13 by treating them with ethyl cyanoacetate 14 in acetic acid followed by hydrolysis with KOH in ethanol and the products were obtained in good yields (Scheme 6). \(^{11}\)

![Scheme 6](image1)

The reaction of chalcones and acetamides is a popular method for decades in the preparation of 2-pyridones. Synthesis of 3-cyano-2-pyridones 18 have been carried out from \(\alpha,\beta\)-unsaturated carbonyl compounds 16 by treating them with cyanoacetamides 17 by Ciufolini et al (Scheme 7). \(^{12}\) This methodology had also been later applied for the synthesis of natural product Nothapodytine B.

![Scheme 7](image2)

A simple synthesis of novel 2-pyridones from chalcones was put forward by Mohammad Al-Arab. \(^{13}\) Recently, Rong et al. have put forward a facile method for the synthesis of 1,2-dihydro-2-oxo-4,6-diarylpyridine-3-carbonitrile from cyanoacetamides and enecarbonyl compounds under solvent free conditions. \(^{14},^{15}\) Such compounds have found applications in the synthesis of some natural products like Nothapodytine B. \(^{16}\) 2-Pyridones 20 have also been synthesized from enaminoketones 19 and cyanoacetamide in the presence of strong basic catalysts such as sodium hydride or alkoxides by Keshk et al (Scheme 8). \(^{17}\)
Dong and coworkers have reported a facile and efficient synthesis of halogenated pyridine-2(1H)-ones 22 from a series of readily available enaminones 21 under Vilsmeier-Haack reaction condition. The report has shown a series of halogenation, formylation and intramolecular nucleophilic cyclization under Vilsmeier-Haack reaction condition shows the importance of the reaction in the synthesis functionalized heterocycles (Scheme 9).

A readily available starting material like 1-acetyl,1-carbamoylcyclopropanes 23 were efficiently converted to pyridin-2(1H)-ones 24 and 25 by Vilsmeier-Haack reaction. The mechanism of the formation of the pyridine derivatives shows sequential ring opening, haloformylation and intramolecular cyclization. A slight change in the reaction condition gave different product from the same substrate, indicates that Vilsmeier-Haack reaction can be effectively used for the synthesis of highly functionalized heterocycles (Scheme 10).
Kohler et al have discussed the reactions of δ-ketonitriles and their further conversion to 2-pyridones under basic conditions in 1922 itself (Scheme 11).^{19}

Synthetic potential of β-substituted vinamidinium hexafluorophosphate salts 29 have been effectively utilized by Marcoux et al for the preparation of 3,5-substituted 2-pyridone 30 (Scheme 12),^{20} β-substituted vinamidinium hexafluorophosphate salts 29 in turn have been prepared by the Vilsmeier-Haack reaction of acetic or substituted acetic acids or their acid chlorides.

Ring expansion reactions can also be used to synthesize 2-pyridone derivatives. This technique is used in the synthesis of 2-pyridone derivatives 32 and 34 from substituted oxazoles 31 and 33 (Scheme 13 & 14) respectively.^{21}
Reactions of various alkenes or alkynes with carbonyl compounds afford 2-pyridone derivatives. Duchene et al have shown that (Z)-3-substituted-3-iodoprop-2-enamides 36 can be synthesized from (Z)-iodovinyllic acids 35 when cross-coupled with tributylstannylallenes, which resulted in a one-pot synthesis of 4,6-disubstituted-2-pyridones 37 (Scheme 15).²²

Libraries of 3,5,6-trisubstituted-2-pyridone derivatives are generated by rapid microwave assisted solution phase methods using a one-pot, two-step protocol.²³ The three-component condensation of CH–acidic carbonyl compounds 38, N,N-dimethylformamide dimethylacetal 39 and methylene active nitriles, leads to the formation of 2-pyridones 41 and fused analogues in moderate to good yields and high purities (Scheme 16).
Very recently Rao *et al.* have described a facile one pot method for the synthesis of novel 3,5,6-trisubstituted-2-pyridones 44 from the acetylated Baylis–Hillman esters 43 and β-enamino esters or β-enaminonitriles 42 (Scheme 17).\(^{24}\)

**Scheme 17**

Reaction of amines with an allenic precursor 45 afforded aminoarylpyridones 46 in good yields (Scheme 19).\(^{25}\) These syntheses can be performed in two distinct steps, allowing the possibility to introduce different substituents in the positions 1 and 4 (Scheme 18).

**Scheme 18**

Trimethylsilylketene 48 reacts with acyl isocyanates 47 to give 4-trimethylsiloxy-1,3-oxazin-6-ones 49 which smoothly undergo the Diels-Alder reaction with dimethyl acetylenedicarboxylate 50 or methyl propiolate to furnish 2-pyridones 51 (Scheme 19).\(^{26}\)
4-Trimethylsiloxy-1,3-oxazin-6-ones 49 smoothly react with enamines 52 of cycloalkanones to give bicyclic 2-pyridones 53 (Scheme 20). 27

Allavi and coworkers have described a new modular synthesis of deoxypyrindinoline in which 4,5-disubstituted 3-hydroxy pyridine as the key intermediate. In this synthesis the pyridine ring was constructed by a series of reactions. The allylamine 54 was allowed to react with 2 equivalents of bromoketone 55 into a pyridinium derivative 57, which was deallylated using titanium II compound, generated from titanium isopropoxide and propylmagnesium bromide for the intermediate substituted 3-hydroxypyridine 58 (Scheme 21). 3
A new synthetic route for the biologically important imidazo[4,5-b]pyridine ring 62 system is described by Tenant et al.\(^4\) Readily available 5-chloro-4-nitroimidazole was converted into its acid chloride derivatives 60 by known chemistry. It was then treated with a variety of \(\beta\)-keto esters. The resulting compounds 61 were subjected to reductive cyclizations to imidazo[4,5-b]pyridinones 62 by catalytic hydrogenation in ethanol over palladium on charcoal or by treatment of alkaline sodium borohydride in the presence of palladium. Highly oxygenated derivatives of 1-deazapurines are thus readily available by this method (Scheme 22).

Scheme 21

Scheme 22
For the preparation of a pyridone derivative, an intramolecular Michael-type addition followed by retro-Michael elimination was reported during the total synthesis of a naturally occurring alkaloid (-)-Myrtine. (S,S,R)- (+)-N-Sulfinyl-α-amino-α-ketophosphonate 63, was treated with dimethylformamide dimethylacetal at room temperature for 12 h. The resulting enaminone 64 was treated with 4N HCl and isolated the pyridone derivative 65 in excellent yields (Scheme 23).  

Scheme 23

Alkylsulfonyl-substituted pyridones have been obtained from ketene dithioacetals in high yields. α-Oxoketene dithioacetals 66 when treated with cyanoacetamide in the presence of sodium isopropoxide afforded 2-pyridones 67 in good yields (Scheme 24). An inseparable 4-ethoxy and 4-methylthiopyridones were obtained in the same reaction when sodium ethoxide was used instead of sodium isopropoxide.

Scheme 24

Fused pyridones 69 have been obtained in a double cyclization process involving substitution of 4-methylthio substituent of the pyridone ring by a second molecule of the cyanoacetamide during the reaction of 68 with secondary α-cyanoacetamides (Scheme 25). With α-oxoketene-N,S-acetals, the reaction produces 3-cyano-4-aminopyridones in moderate to good yield.
Scheme 25

N-Substituted pyridones 71 were obtained when secondary α-cyanoacetamide derivatives were reacted with 2-cyano-3,3-bis(methylthio) acrylonitrile 70 in DMF or in acetonitrile containing K$_2$CO$_3$ (Scheme 26).³⁰

Scheme 26

N-Amino-2-pyridones 73 were obtained when ketene dithioacetal 72 reacted with cyanoacetohydrazide at room temperature in the presence of potassium hydroxide in 1,4-dioxane (Scheme 27).³¹

Scheme 27

Junjappa et al have shown that polarized dienes 75, obtained by the 1,2-addition of Reformatsky reagent to α-oxoketene dithioacetals 74, when heated with ammonium acetate/acetic acid buffer afford substituted 2-pyridones 76 (Scheme 28).³²
Similarly, 2-pyridone derivatives 78 were afforded in good yields by the acid hydrolysis of ketene dithioacetals of alkylidene malononitrile 77 (Scheme 29). 33

\[
\text{\textbf{Scheme 29}}
\]

\(\alpha\)-Oxoketene-\(N,S\)-acetals 79 react with malonyl chloride 80 to afford 4-hydroxy-6-(methylsulfanyl)-2(1H)-pyridones 81 (Scheme 30) in good yields. 34

\[
\text{\textbf{Scheme 30}}
\]

A one-pot synthesis of 6-methylthio-\(N\)-aryl-2-pyridone 84 and its deazapurine analogues by the reaction of ketene dithioacetal 82 with substituted acetanilides 83, has been reported by Elgemee et al (Scheme 31). 35

\[
\text{\textbf{Scheme 31}}
\]

Synthesis of 2-pyridones 87 can also be carried out using ketene-\(N,N\)-aminals 85 on heating with methyl propiolate 86 in methanol (Scheme 32). 36
We have described the formation of 2-aryloxy-2-[3,3-bis(methylsulfanyl)-2-propylidene]malononitriles \(^{89}\) from 2-aryloxy-3,3-bis(methylsulfanyl)acrylaldehydes \(^{88}\) and their cyclization reactions in the presence of bromine in chloroform or hydrochloric acid in tertiary butanol to afford 5-aryloxy-2-oxo-1,2-dihydro-3-pyridinecarbonitriles \(^{90}\) (Scheme 33).\(^{37}\)

**Scheme 33**

Similar pyridones \(^{90}\) can also be synthesized by treating 2-aryloxy-3,3-bis(methylsulfanyl)acrylaldehydes \(^{88}\) with cyanoacetamides (Scheme 34).\(^{38}\)

**Scheme 34**

We have reviewed important reactions for the synthesis of 2-pyridones and hydroxypyridines in this section. Most of the reactions involve the reaction of a nitrogen containing binucleophile with bielectrophile. The reactions of chalcones with cyanoacetamides and malononitriles have been extensively studied for the
preparation of 2-pyridones. Still the synthesis of β-chloroenones and their further transformation to 2-oxo/2-hydroxy-5,6-bisarylnicotinonitriles deserve much attention, as the main challenge to synthetic chemist is the synthesis of molecules in good yields with appropriate functional moieties at suitable position of the carbon skeleton.

5.3. Results and discussions

5.3.1. Reactions of 3-chloro-1,2-diaryl-2-propen-1-ones with malononitrile: synthesis of 2-hydroxy-5,6-diarylnicotinonitriles

Initially we investigated the reaction of 3-chloro-1,2-diphenyl-2-propen-1-one 92a with malononitrile in ammonium acetate/acetic acid buffer. The optimization studies are concluded in Table 1. All the reactions were monitored by TLC, by a 7 GF silica gel stationary phase, for every half an hour.

Table 1 Optimization studies for the synthesis of 2-hydroxy-5,6-diphenylnicotinonitrile 93a

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Temperature-Time</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>room temperature-10hrs</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>40°C-10hrs</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>60°C-10hrs</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>70°C-15hrs</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>72°C-15hrs</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>74°C-15hrs</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>76°C-12hrs</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>78°C-8hrs</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>80°C-8hrs</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>90 °C-3h</td>
<td>Complex reaction mixture</td>
</tr>
</tbody>
</table>

------------------------------------------------------------------------------
From the table it is clear that 3-chloro-1,2-diphenyl-2-propen-1-one 92a is unreactive with malononitrile at room temperature or at a temperature below 70°C. The 2-hydroxy-5,6-diphenylnicotinonitrile 93a, having melting point 182-184°C, was obtained in 85 % yield when the reaction was conducted at 78 °C for 8h (Scheme 35).

Scheme 35

2-Hydroxy-5,6-diphenylnicotinonitrile 93a was characterized on the basis of conventional spectroscopic methods and Single crystal X-ray analysis. In the IR spectrum, the compound 93a showed characteristic OH and NH stretching at 3463 cm⁻¹, 3433 cm⁻¹ and 3352 cm⁻¹ due to the pyridine-pyridone equilibrium. Aromatic C-H stretching was observed at 3178 cm⁻¹. Characteristic cyan group peak observed at 2216 cm⁻¹ and the carbonyl stretching at 1645 cm⁻¹. The C=N and C-N stretching was observed at 1591 cm⁻¹ and 1463 cm⁻¹. The C=C stretching was observed at 1627, 1591, 1544 cm⁻¹ of both aromatic and pyridine rings respectively. The GCMS of the compound showed the molecular ion peak at m/z 272 and the base peaks at m/z 270 and 271 respectively. The ¹H NMR spectrum of the compound showed two aromatic proton singlets at δ 7.75 and δ 7.65 respectively corresponding to the pyridinyl protons of the two tautomers. Two multiplets were appeared at δ 6.92-6.97 and 7.05-7.1 in which each peak corresponds to two hydrogens atoms in the phenyl rings. Other aromatic protons appeared are 7.11-7.19 as a 5 hydrogen multiplet and 7.21-7.34 as an 11 hydrogen multiplet respectively. The hydroxyl and amino protons found to be merged at δ 5.25 as a two proton broad signal. The ¹³C NMR spectrum of the compound has shown a carbonyl carbon peak at δ160.37 due to the pyridone ring carbonyl carbon and the two cyan group signals at 115.79 and 115.49 due to the hydroxypyridine-pyridone equilibrium. The other aromatic and heterocyclic carbons were appeared at
157.71, 150.77, 149.38, 143.52, 138.87, 138.03, 136.41, 131.94, 129.64, 129.55, 129.43, 128.84, 128.77, 128.42, 128.31, 128.15, 127.95, 127.22, 126.84, 116.61, 99.11, 96.41, 89.87, 77.32, 77, 76.68 and 74.15 ppm. The CHN analysis of the compound 93a gave the percentage of various elements presented in the molecule as Carbon = 79.385, Hydrogen = 4.33, Nitrogen = 10.295, which are found to be agreeing with the calculated data as Carbon-79.39, Hydrogen-4.44, Nitrogen-10.29 and confirmed the molecular formula as C_{18}H_{12}N_{2}O. Literature review supports the above spectral data as 2-pyridones usually exist in 2-pyridone/2-hydroxy pyridine equilibrium.40

![Figure 1 IR spectrum of 2-hydroxy-5,6-diphenylnicotinonitrile 93a](image-url)
**Figure 2** GCMS spectrum of 2-hydroxy-5,6-diphenylnicotinonitrile 93a

**Figure 3** $^1$HNMR spectrum of spectrum of 2-hydroxy-5,6-diphenylnicotinonitrile 93a
The proposed mechanism of the reaction is as follows: Initially the β-chloroenone underwent Knoevenagel reaction with malononitrile in the presence of ammonium acetate/acetic acid mixture to get an adduct 94. The alkylidenemalononitrile formed then, underwent an intramolecular addition-elimination reaction followed by hydroxylation to get 2-hydroxypyridine. Due to the comparable stability of the 2-pyridone ring systems in its crystal lattice, 2-hydroxypyridine exists as 2-hydroxypyridine/2-pyridone tautomeric mixture (Scheme 36).
The reaction was extended to other substituted β-chloroenones to get a series of functionalized nicotine derivatives (Scheme 37) (Table 1). All the products were obtained in moderate to good yields. Both 3-chloro-1-(2-methoxyphenyl)-2-phenyl-2-propen-1-one and 3-chloro-2-(2-chlorophenyl)-1-(4-methylphenyl)-2-propen-1-one did not undergo the reaction and starting materials were isolated.
Table 1 Synthesis of 5,6-diaryl-2-hydroxynicotinonitriles 93a-k

<table>
<thead>
<tr>
<th>93</th>
<th>R₁</th>
<th>R2</th>
<th>Yields %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>85</td>
</tr>
<tr>
<td>b</td>
<td>Br</td>
<td>H</td>
<td>75</td>
</tr>
<tr>
<td>c</td>
<td>4-OC₃H₃</td>
<td>H</td>
<td>82</td>
</tr>
<tr>
<td>d</td>
<td>4-Cl</td>
<td>H</td>
<td>88</td>
</tr>
<tr>
<td>e</td>
<td>4-CH₃</td>
<td>H</td>
<td>78</td>
</tr>
<tr>
<td>f</td>
<td>4-Cl</td>
<td>2-Cl</td>
<td>82</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>2-Cl</td>
<td>77</td>
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<tr>
<td>h</td>
<td>4-CH₃</td>
<td>4-OC₃H₃</td>
<td>71</td>
</tr>
<tr>
<td>i</td>
<td>4-CH₃</td>
<td>2-Cl</td>
<td>0</td>
</tr>
<tr>
<td>j</td>
<td>2-OC₃H₃</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>k</td>
<td>H</td>
<td>4-OC₃H₃</td>
<td>90</td>
</tr>
</tbody>
</table>

5.3.2 Crystal structure and structure refinement of 2-hydroxy-5-(4-methoxyphenyl)-6-phenylnicotinonitrile 93k

The structure refinement on 93k showed that the compound exits as 2-hydroxy-5-(4-methoxyphenyl)-6-phenylnicotinonitrile (molecular formula: C₁₉H₁₂N₂O) in its crystal lattice (Figure 5, 6 & 7). The crystal parameters are as follows: Space group, P 2₁/c; a, 12.0731 (14); b, 14.1000 (17); c, 9.8157 (12); α, 90.00; β, 108.797 (7); γ, 90.00; V, 1581.82, Z, Z'= Z: 4, Z': 0, R-Factor [%] = 5.91 and CCDC 791271. Two neighboring molecules are bound together with intermolecular hydrogen bonding (N-H-O) between adjacent hydroxyl pyridine moieties (Figure 7). Another important hydrogen bonding was observed between the nitrogen atom of the cyano group and the hydrogen atom presented at the para position of the nicotinonitrile. The molecule is arranged in the three dimensional crystal lattice due to the aromatic stacking interactions and weak polar interactions between methoxy groups and aromatic stacking interactions (Figure 5, 6 & 7). Various
bond lengths obtained by the analysis according to the atoms shown in Figure 5 is displayed in Table 2 and the bond lengths obtained are in mutual agreement with earlier reported values.

**Figure 5** Ortep diagram of 2-hydroxy-5-(4-methoxyphenyl)-6-phenylnicotinonitrile 93k with atom label

**Figure 6** Ortep diagram of 2-hydroxy-5-(4-methoxyphenyl)-6-phenylnicotinonitrile 93k
Figure 7 Three dimensional arrays of 2-hydroxy-5-(4-methoxyphenyl)-6-phenylnicotinonitrile in its crystal lattice 93k

Table 2: Bond lengths of various bonds presents in 2-hydroxy-5-(4-methoxyphenyl)-6-phenylnicotinonitrile 93k obtained from Single Crystal Analysis

<table>
<thead>
<tr>
<th>No.</th>
<th>Atom 1</th>
<th>Atom 2</th>
<th>Bond length (Å unit)</th>
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<tbody>
<tr>
<td>1.</td>
<td>N2</td>
<td>C13</td>
<td>1.351</td>
</tr>
<tr>
<td>2.</td>
<td>N2</td>
<td>C12</td>
<td>1.344</td>
</tr>
<tr>
<td>3.</td>
<td>C8</td>
<td>C13</td>
<td>1.399</td>
</tr>
<tr>
<td>4.</td>
<td>C8</td>
<td>C9</td>
<td>1.394</td>
</tr>
<tr>
<td>5.</td>
<td>C8</td>
<td>C5</td>
<td>1.489</td>
</tr>
<tr>
<td>6.</td>
<td>C10</td>
<td>C12</td>
<td>1.414</td>
</tr>
<tr>
<td>7.</td>
<td>C10</td>
<td>C9</td>
<td>1.389</td>
</tr>
<tr>
<td>8.</td>
<td>C10</td>
<td>C11</td>
<td>1.425</td>
</tr>
<tr>
<td>9.</td>
<td>C13</td>
<td>C14</td>
<td>1.482</td>
</tr>
<tr>
<td>10.</td>
<td>C12</td>
<td>O2</td>
<td>1.375</td>
</tr>
<tr>
<td>11.</td>
<td>C9</td>
<td>H9</td>
<td>0.930</td>
</tr>
<tr>
<td>12.</td>
<td>C14</td>
<td>C15</td>
<td>1.388</td>
</tr>
<tr>
<td>13.</td>
<td>C14</td>
<td>C19</td>
<td>1.397</td>
</tr>
<tr>
<td>14.</td>
<td>C5</td>
<td>C6</td>
<td>1.392</td>
</tr>
</tbody>
</table>
5.3.3. Reactions of 3-chloro-1,2-diaryl-2-propen-1-ones with cyanoacetamide

As a continuation to earlier studies in our laboratory, 3-chloro-2,3-diarylpropan-1-ones were treated with cyanoacetamide in the presence of ammonium acetate/acetic acid mixture at 78°C. The reaction afforded a complex
mixture of products and found difficulty in exploring the reaction for the synthesis of pyridine derivatives.

5.4 Conclusion

The synthesis of functionalized 2-hydroxy-5,6-diaryl nicotinonitriles from 3-chloro-1,2-diaryl-2-propen-1-ones is found to be very efficient and it can be considered as a general method for the synthesis of pyridine derivatives.

5.5. Experimental

Melting points were determined on a Buchi 530 melting point apparatus and were uncorrected. The IR spectra were recorded by KBr pellet method on a Shimadzu FTIR 470 spectrometer and the frequencies are reported in cm$^{-1}$. Mass spectra were recorded on a GCMS Shimadzu 5050 model instrument. $^1$H NMR spectra were recorded on a Bruker EM 400 MHz spectrometer using CDCl$_3$ as the solvent. $^{13}$C NMR spectra were recorded on a Bruker EM 400 MHz spectrometer using CDCl$_3$ as the solvent. Both $^{13}$C NMR and $^1$H NMR values are expressed in $\delta$ (ppm). Elemental analyses were done on a Shimadzu CHN analyzer.

All reagents were commercially available and were purified before use. All the solvents used were dried and distilled under reduced pressure. 3-Chloro-1,2-diaryl-2-propen-1-ones were prepared according to the procedure explained in Chapter 3 of this thesis. All the purified compounds gave single spot upon TLC analyses on silica gel 7GF using ethyl acetate/hexane as eluent. Iodine vapors or KMnO$_4$ in water was used as the developing agent for TLC.

5.5.1. General procedure for the synthesis of 5,6-diairyl-2-hydroxy- nicotinonitriles

In a 250 ml R. B. flask fitted with a guard tube and a bar magnet inside, a mixture of malononitrile (0.950 g, 14.4 mmol), ammonium acetate (2.96 g, 38.4 mmol) and acetic acid (9.6 ml) were taken and refluxed with stirring for 10 min at 70 $^0$C. To this 3-chloro-1,2-diaryl-2-propen-1-one (9.6 mmol) was added and stirring was continued for 8 hrs. The reaction was monitored by TLC and after complete consumption of the starting material; it was allowed to cool up to room temperature and poured into ice cold water. Extracted with chloroform (25 x 3), washed with
water (25 x 3), dried over anhydrous sodium sulfate and the chloroform layer was evaporated to afford the crude product. The crude product was subjected to column chromatography over 60-120 mesh silica gel using ethyl acetate : hexane (1:9) as eluent and the products were isolated in pure and better yields.

**2-Hydroxy-5,6-diphenylnicotinonitrile 93a** was obtained by the reaction of 3-chloro-1,2-diphenyl-2-propen-1-one 92a (2.32 g, 9.6 mmol) with malononitrile (0.950 g, 14.4 mmol) in the presence of ammonium acetate (2.96 g, 38.4 mmol) and acetic acid (9.6ml) at 78°C as a pale yellow powder; mp, 182-184°C; yield, 2.22 g (85 %); IR (KBr, ν max) = 3463 (OH), 3284 (NH), 1654 (CO), 1627 (C=C) cm⁻¹; GCMS (m/z) = 272 (M⁺), 271 (base peak), 270, 253, 226, 135.2, 140, 121.5, 94.5, 77; ¹H NMR (400 MHz, CDCl₃) δ = 5.25 (2H, broad, NH and OH), 6.92-6.97 (2H, m, ArH), 7.05-7.1 (2H, M, ArH), 7.11-7.19 (5H, m, ArH), 7.21-7.34 (11H, m, ArH), 7.65 (1H, s, pyridine ring hydrogen), 7.75 (1H, s, pyridine ring hydrogen); ¹³C NMR (400 MHz, CDCl₃) δ = 160.37 (CO), 157.71, 150.77, 149.38, 143.52, 138.87, 138.03, 136.41, 131.94, 129.64, 129.55, 129.43, 128.84, 128.77, 128.42, 128.31, 128.15, 127.95, 127.22, 126.84, 116.61, 115.79 (CN), 115.49 (CN), 99.11, 96.41, 89.87; Anal Calcd. for C₁₈H₁₂N₂O: Carbon-79.39; Hydrogen-4.44; Nitrogen-10.29. Found: Carbon = 79.385; Hydrogen = 4.33; Nitrogen = 10.295.

**6-(4-Bromophenyl)-2-hydroxy-5-phenylnicotinonitrile 93b** was obtained by the reaction between 1-(4-bromophenyl)-3-chloro-2-phenyl-2-propen-1-one 92b (3.08 g, 9.6 mmol) with 1.5 equivalent malononitrile (0.950 g, 14.4 mmol) in ammonium acetate (2.96 g, 38.4 mmol) and acetic
acid (9.6ml) mixture at 78°C as a pale yellow powder, melting point = 204-206°C. Yield = 2.53 g (75 %); IR (KBr, ν max) = 3402 (OH), 3342 (NH), 3150 (aromatic C-H), 3050 (aromatic C-H), 2221 (CN), 1656 (C=O), 1587 (C=N), 1544 (C=N), 1469 (C=C), 1390 (C-C) cm⁻¹; GCMS (m/z) = 353(M+2)+, 352 (M+2)+, 351 (M+1)+, 350 (M)+, 288, 286, 270 (base peak), 255, 242, 227, 214, 184, 156, 140, 75; ¹H NMR (400 MHz, CDCl₃) δ = 7.739 (1H, s, pyridine ring hydrogen), 7.64 (1H, s, pyridine ring hydrogen), 7.43 (4H, d, J = 10 Hz, ArH), 7.16-7.23 (5H, m, ArH), 7.025 (4H, d, J = 10 Hz, ArH), 6.91-6.97 (3H, m, ArH), 5.83 (2H, Broad, NH and OH); ¹³C NMR (400 MHz, CDCl₃) δ = 207, 157.67, 150.85, 147.9, 143.72, 138.24, 137.94, 137.55, 135.26, 131.71, 131.62, 131.33, 131.18, 129.39, 129.31, 128.62, 128.35, 127.43, 126.69, 123.37, 116.44, 115.63 (CN), 115.35 (CN), 98.68, 96.7, 90.14.

2-Hydroxy-6-(4-methoxyphenyl)-5-phenylnicotinonitrile 93c was obtained by the reaction between 3-chloro-1-(4-methoxyphenyl)-2-phenyl-2-propen-1-one 92c (2.61 g, 9.6 mmol) with 1.5 equivalent malononitrile (0.950 g, 14.4 mmol) in ammonium acetate (2.96 g, 38.4 mmol) and acetic acid (9.6ml) mixture at 78°C as a pale yellow powder, melting point = 178-180°C; Yield = 2.38 g (82 %); IR (KBr, ν max) = 3413 (OH), 3348 (NH), 3249 (aromatic C-H), 3060 (aromatic C-H), 3028 (aromatic C-H), 3002 (aromatic C-H), 2217 (CN), 1660 (C=O), 1602 (C=N), 1512, 1492, 1452, 1425 cm⁻¹; GCMS (m/z) = 325 (M+Na⁺, base peak)+, 309, 294, 281, 265, 227, 155, 141, 127, 114, 100; ¹H NMR (400 MHz, CDCl₃) δ = 8.01 (1H, s, pyridine ring hydrogen), 7.63 (1H, s, pyridine ring hydrogen), 7.194 (2H, ArH), 7.069 (2H, d, ArH), 6.954 (8H, d, J = 8.8 Hz, ArH),
6.81 (2H, dd, ArH), 3.885 (3H, OMe), 3.793 (3H, s, OMe); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ = 171.5, 164, 132.36, 131.05, 129.45, 128.24, 121.6, 113.78 (CN), 113.74 (CN), 55.49.

6-(4-Chlorophenyl)-2-hydroxy-5-phenyl nicotinonitrile

93d was obtained by the reaction between 3-chloro-1-(4-chlorophenyl)-2-phenyl-2-propen-1-one 92d (2.65 g, 9.6 mmol) with 1.5 equivalent malononitrile (0.950 g, 14.4 mmol) in ammonium acetate (2.96 g, 38.4 mmol) and acetic acid (9.6ml) mixture at 78$^0$C as a pale yellow powder, melting point = 200-202$^0$C. Yield = 2.59 g (88 %); IR (KBr, $\nu$ max) = 3407(OH), 3342(NH), 3232 (aromatic C-H), 2219 (CN), 1649 (C=O), 1591 (C=C) cm$^{-1}$; GCMS (m/z) = 308 (m+2), 307 (m+1), 306 (m+), 305 (base peak), 304, 269, 253, 252, 226, 214, 134, 121, 107; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.71 (1H, s, pyridine ring hydrogen), 7.65 (1H, s, pyridine ring hydrogen), 7.25-7.29 (4H, m, ArH), 7.17-7.22 (6H, m, ArH), 7.05-7.11 (4H, m, ArH), 6.91-6.96 (3H, m, ArH), 5.3 (2H, broad, OH and NH); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ = 158.88, 157.66, 150.82, 147.94, 143.71, 138.22, 137.99, 137.59, 137.24, 135.11, 134.97, 134.79, 131.84, 131.09, 130.95, 129.4, 129.33, 128.85, 128.7, 128.63, 128.36, 128.2, 127.44, 126.76, 116.46, 115.64 (CN), 115.36 (CN), 98.81, 96.72, 90.14.

2-Hydroxy-6-(4-methylphenyl)-5-phenyl nicotinonitrile

93e was obtained by the reaction between 3-chloro-1-(4-methylphenyl)-2-phenyl-2-propen-1-one 92e (2.46 g, 9.6 mmol) with 1.5 equivalent malononitrile (0.950 g, 14.4 mmol) in ammonium acetate (2.96 g, 38.4 mmol) and acetic acid (9.6ml) mixture at 78$^0$C as a pale yellow powder,
melting point = 178-180°C. Yield = 2.14 g (78%); IR (KBr, v max) = 3456 (OH), 3402 (NH), 3350 (NH), 3340 (OH), 3249 (aromatic C-H), 3056 (aromatic C-H), 3029 (aromatic C-H), 2223(CN), 1656 (CO), 1649 (C=N), 1589 (C=C), 1546 (C=C) cm⁻¹; GCMS (m/z) = 286 (M⁺), 285, 284 (base peak), 269, 252, 240, 227, 207, 141, 128, 101; ¹H NMR (400 MHz, CDCl₃) δ = 7.9 (4H, d, j = 10Hz, ArH), 7.72 (1H, s, pyridine ring hydrogen), 7.63 (1H, s, pyridine ring hydrogen), 7.26-7.15 (5H, m, ArH), 7.02 (4H, d, j = 10Hz, ArH), 6.93-6.97 (3H, m, ArH), 5.24 (4H, broad, OH and NH), 2.3185 (6H, s, CH₃); ¹³C NMR (400 MHz, CDCl₃) δ = 160, 157, 150.8, 149.55, 143.49, 138.83, 138.11, 138.02, 133.41, 131.91, 129.61, 129.44, 129.04, 128.67, 128.43, 128.15, 127.14, 115.88 (CN), 115.7 (CN), 99.14, 96.12, 89.1, 21.3.

5-(2-Chlorophenyl)-6-(4-chlorophenyl)-2-hydroxynicotinonitrile 93f was obtained by the reaction between 3-chloro-2-(2-chlorophenyl)-1-(4-chlorophenyl)-2-propen-1-one 92f (2.98 g, 9.6 mmol) with 1.5 equivalent malononitrile (0.950 g, 14.4 mmol) in ammonium acetate (2.96 g, 38.4 mmol) and acetic acid (9.6ml) mixture at 78°C as a pale yellow powder, melting point = 178-180°C. Yield = 2.68 g (82%); IR (KBr, v max) = 3417(OH), 3342(NH), 3245 (aromatic C-H), 3184 (aromatic C-H), 2221 (CN), 1649 (C=O) cm⁻¹; GCMS (m/z) = 344(M+4)⁺, 343 (M+3)⁺, 342 (M+2)⁺, 341 (M+1)⁺, 340 (M)⁺, 339 (base peak), 316, 325, 324, 306, 249, 230, 168, 112, 76; ¹H NMR (400 Mhz, CDCl₃) δ = 7.34-7.28 (2H, m, ArH), 7.27-7.21 (3H, m, ArH), 7.21-7.16 (2H, m, ArH), 7.14-7.07 (5H, m, ArH), 6.95-6.91 (2H, m, ArH), 5.35 (2H, broad, OH and NH); ¹³C NMR (400 Mhz, CDCl₃) δ = 162.1, 161.8, 152.09, 145.67, 140.66,
140.06, 139.5, 135.87, 134.76, 133.21, 132.55, 132.45, 132, 130.4, 130.04, 129.7, 128.99, 128.76, 128.53, 128.23, 125.4, 119.05, 116.07, 114.3 (CN), 114.8 (CN), 102.9, 96.78.

5-(2-Chlorophenyl)-2-hydroxy-6-phenylnicotinonitrile
93g was obtained by the reaction between 3-chloro-2-(2-chlorophenyl)-1-phenyl-2-propen-1-one 92g (2.65 g, 9.6 mmol) with 1.5 equivalent malononitrile (0.950 g, 14.4 mmol) in ammonium acetate (2.96 g, 38.4 mmol) and acetic acid (9.6ml) mixture at 78°C as a pale yellow powder, melting point = 132-134°C. Yield = 2.26 g (77 %); IR (KBr, v max) = 3417(OH), 3340(NH), 3244 (aromatic C-H), 3056 (aromatic C-H), 2219 (CN), 1650 (C=O) cm⁻¹; GCMS (m/z) = 308 (M+2)⁺, 307 (M+1)⁺, 306 (M)⁺, 305, 304, 281, 270, 253, 242, 226, 207, 191, 174, 147, 134, 121, 107, 94, 83 (base peak); ¹H NMR (400 MHz, CDCl₃) δ = 7.55 (1H, s, pyridine ring hydrogen), 7.27-7.31 (2H, m, ArH), 7.13-7.18 (2H, m, ArH), 7.02-7.09 (10H, m, ArH), 6.9-6.94 (2H, m, ArH), 5.3461 (2H, broad, OH and NH); ¹³C NMR (400 MHz, CDCl₃) δ = 151.31, 150.37, 138.84, 138.45, 136.82, 133.49, 133, 132.04, 129.42, 129.1, 128.96, 128.78, 126.41, 115.74 (CN), 115.56 (CN), 98.7, 95.69.

2-Hydroxy-5-(4-methoxyphenyl)-6-(4-methylphenyl)nicotinonitrile 93h was obtained by the reaction between 3-chloro-2-(4-methoxyphenyl)-1-(4-methylphenyl)-2-propen-1-one 92h (2.75 g, 9.6 mmol) with 1.5 equivalent malononitrile (0.950 g, 14.4 mmol) in ammonium acetate (2.96 g, 38.4 mmol) and acetic acid (9.6ml) mixture at 78°C as a deep yellow powder, melting point = 188-190°C. Yield = 2.15 g (71 %); IR (KBr, v max) = 3481(OH), 3363(NH), 3234, 3014 (aromatic C-H), 2217
(CN), 1631 (C=O) cm⁻¹; GCMS (m/z) = 316 (M)⁺, 315 (base peak), 314, 300, 285, 271, 257, 256, 239, 227, 207, 191, 170, 150, 135, 128, 101, 88; ¹H NMR (400 MHz, CDCl₃) δ = 7.6 (1H, s, pyridine ring hydrogen), 7.11 (4H, d, j = 10 Hz, ArH), 7.03 (4H, d, j = 10 Hz, ArH), 6.86 (4H, d, j = 10 Hz, ArH), 6.7 (4H, d, j = 10 Hz, ArH), 5.22 (2H, broad, OH and NH), 3.75 (6H, s, OMe), 2.33 (6H, s, CH₃); ¹³C NMR (400 MHz, CDCl₃) δ = 170.47, 163.93, 155.74, 150.55, 149.43, 138.71, 137.94, 133.58, 132.28, 131.61, 130.51, 130.41, 130.19, 129.41, 129.23, 129.08, 127.89, 126.52, 122.75, 121.61, 117.52, 115.95, 115.75, 114.82 (CN), 113.71 (CN), 113.59, 99.14, 96.10.

2-Hydroxy-5-(4-methoxyphenyl)-6-phenylnicotinonitrile 93k was obtained by the reaction between 3-chloro-2-(4-methoxyphenyl)-1-phenyl-2-propen-1-one 92k (2.61 g, 9.6 mmol) with 1.5 equivalent malononitrile (0.950 g, 14.4 mmol) in ammonium acetate (2.96g, 38.4 mmol) and acetic acid (9.6ml) mixture at 78°C as a pale yellow powder, melting point = 204-206°C; Yield = 2.61 g (90 %); IR (KBr, ν max) = 3479 (OH), 3296 (NH), 3186 (aromatic C-H), 2212 (CN), 1620 (CO) cm⁻¹; GCMS (m/z) = 302 (m+), 301, 300, 287, 286, 285, 270, 214, 207, 143, 128, 89, 76; ¹H NMR (400 MHz, CDCl₃) δ = 3.74 (3H, s, OMe), 3.79 (3H, s, OMe), 5.2 (2H, broad, NH and OH), 6.7 (1H, s, dd, ArH), 6.78 (2H, m, ArH), 6.86 (1H, dd, ArH), 6.98 (2H, m, ArH), 7.14 (1H, dd, ArH), 7.1-7.34 (6H, m, ArH), 7.63 (1H, s, pyridine ring hydrogen), 7.72 (1H, s, pyridine ring hydrogen); ¹³C NMR (400 MHz, CDCl₃) δ = 160.23 (CO), 158.79, 157.52, 150.54, 149.23, 144.25, 143.38, 142.04, 139.04, 137.97, 136.6, 131.58, 130.51, 130.45, 130.22, 129.57, 129.51, 128.74, 128.65, 128.33, 127.96, 126.46.
116.67, 115.86, 115.54, 113.88 (CN), 113.6 (CN), 104.24, 99.08, 96.37, 89.84, 77.32, 77, 76.68, 67.57, 61.22, 55.19, 43.44, 39.31, 30.87; Single Crystal Data: CCDC = 791271, molecular formula = C$_{19}$H$_{12}$N$_{2}$O, space group = P 2$_{1}$/c, Cell lengths = a 12.0731(14) b 14.1000(17) c 9.8157(12), Cell angles = $\alpha$90.00 $\beta$108.797(7) $\gamma$90.00, cell volume = 1581.82, Z, Z$^{'}$ = Z : 4, Z$^{'}$ : 0, R-Factor[%] = 5.91.
5.6. References


