Chapter 4

Lewis Acid Mediated Michael Reaction of Malononitrile with Chalcones: A Novel Strategy for the Synthesis of 2-Chloropyridines and 2-Pyridones

4.1. Introduction

As a continuation to ongoing studies in our laboratory, chalcones were treated with malononitrile under Vilsmeier-Haack reaction condition to afford substituted dihydropyridines, which were readily aromatized to get substituted 2-chloronicotinonitriles. Mechanistic studies on the reaction proved that malononitrile is added to chalcones even in the presence of POCl₃ leading to the formation of 2-pyridones. Besides, chalcones which were reluctant to undergo Vilsmeier-Haack reaction were found to be involved in chloroamination in the presence of Vilsmeier-Haack reagent at higher temperatures to afford chlorovinyl amines. These results are described in the present chapter.

4.2. Lewis acid mediated Michael reaction: An overview

Carbon-carbon bond formation reactions are the most important processes in organic synthesis. An important carbon-carbon bond forming reaction, called Michael reaction involves the conjugate addition of a nucleophile to activated alkenes in the presence of a base. However, the reaction could occur in the presence of Lewis acids, though there are only a
few reports in the literature.\textsuperscript{1} The development of new methods for efficient conjugate addition reactions with a wide range of heteroatom nucleophiles has attracted special attention. The conjugate addition of nitrogen nucleophiles to $\alpha$, $\beta$-enones (aza- Michael reaction) is a widely used method for carbon-nitrogen bond formation. This organic transformation has been especially employed in the synthesis of products generally recognized as building blocks for the preparation of important natural products (Scheme 1).\textsuperscript{2}

\[
\text{Nu :} + \text{R EWG} \xrightarrow{\text{CeCl}_3.7\text{H}_2\text{O}} \text{Nu} \xrightarrow{\text{NaI, Al}_2\text{O}_3} \text{R} \xrightarrow{35^\circ\text{C}, 24\ h} \text{EWG}
\]

**Scheme 1**

Recently Yamagiva reported an enantioselective aza-Michael reaction in the presence of Lewis acid-heterobimetallic cooperative catalyst 6 to get chiral aminoketones 7 (Scheme 2).\textsuperscript{3}

\[
\text{Ph} = \text{MeONH}_2 \xrightarrow{-20^\circ\text{C}} \text{THF} \xrightarrow{6} \text{Ph}
\]

**Scheme 2**

Uraguchi et al have designed a new class of chiral charged Bronsted acids 11 and 12, which found successful application in the development of catalytic enantioselective conjugate addition of arylamines 9 to nitroolefins 8 (Scheme 3).\textsuperscript{4}
Intermolecular cross-double-Michael addition between nitro activated and carbonyl activated olefins 13 and 14 respectively as a new approach in carbon-carbon bond formation has been put forward by Sun et al (Scheme 4).\(^5\)

Scheme 3

Scheme 4

Nakamura et al have reported a double syn-selective Michael addition of enol 17 to enone-Cr complex 16 (Scheme 5).\(^6\)

Scheme 5

Novel Michael additions to phenols promoted by osmium (II) have resulted in a convenient stereoselective synthesis of 2,4- and 2,5-cyclohexadienones (Scheme 6).\(^7\)
Scheme 6

Use of C$_2$-symmetric Cu (II) complexes 26 as chiral Lewis acids in the catalytic enantioselective Michael addition of silylketene acetals 24 to alkylidene malonates 23 have been described by Evans et al in 1994 (Scheme 7).

Scheme 7

Efficient synthesis of 1,3,5-trisubstituted (pyrrol-2-yl)acetic acid esters 29 via dual nucleophilic reactions of sulfonamides or carbamate with 4-trimethylsiloxy-(5E)-hexen-2-ynoates 27 is a good example of Lewis acid catalyzed S$_{N}$1 and intramolecular Michael addition (Scheme 8).
Suga et al have reported asymmetric Michael addition reactions of 2-silyloxyfurans 30 with enamides 31 catalyzed by binaphthylidium-Ni(II) complexes (Scheme 9).  

Scheme 9

Catalytic enantioselective Michael additions of silylenolethers to unsaturated amide derivatives 33 using chiral copper (II) Lewis acid complexes 36 have been reported by Evans et al (Scheme 10).  

Scheme 10

Firouzabadi et al have reported the facile and efficient Michael addition of indoles 37 to α,β-unsaturated electron deficient compounds 38 catalyzed by aluminium dodecyl sulfate trihydrate [Al(DS)₃]·3H₂O in water (Scheme 11).  

Scheme 11

86
Various pyrrole complexes 40 are known to undergo Michael addition with methyl vinyl ketone for further elaboration of the heterocyclic skeleton (Scheme 12).  

![Scheme 12](image)

A novel cyclization reaction of ethanetricarboxylate derivative 43 in the presence of Lewis acids gave oxindole derivatives 44 via Friedel-Crafts intramolecular Michael addition (Scheme 13).

![Scheme 13](image)

Lewis acid catalyzed Michael reactions were widely used for obtaining different indoline alkaloid containing polycyclic architectures (Scheme 14).

![Scheme 14](image)

Jorgenson reported a catalytic asymmetric tandem oxa-Michael addition followed by Friedel-Crafts alkylation reactions to get optically active chromanes (Scheme 15).
It is clear from the literature review that Lewis acid mediated Michael reactions are uncommon and such reactions are important when the reactive species contain base sensitive functional groups. Moreover, such reactions are widely used in asymmetric synthesis and so in the total synthesis of biologically active molecules.

4.3. Results and Discussion

4.3.1. Reactions of chalcones with malononitrile in the presence of Vilsmeier reagent: Synthesis of 4,6-bis(aryl)-2-chloronicotinonitriles 54 a-j

In a pilot experiment 1,1-bis(phenyl)propen-1-one was treated with malononitrile under Vilsmeier-Haack condition. It was unusual to carry out Vilsmeier-Haack reaction at a higher temperatures since DMF could be degraded at higher temperature to get free amines especially dimethyl amine. In the literature, there is only one report on the Vilsmeier-Haack reaction of 2'-aminochalcones providing a mild one-pot synthesis of 2-aryl-4-chloro-N-formyl-1,2-dihydroquinolines\textsuperscript{17} and other chalcones were reluctant to react under Vilsmeier-Haack reaction condition. We expected that 1,1-bis(phenyl)propen-1-one 52a would undergo reaction with malononitrile in the presence of Vilsmeier-Haack reagent to get dihydropyridine 53 (Scheme 16).
However, 1,1-bis(phenyl)propen-1-one \(52a\) was unreactive at room temperature or a temperature below 80°C. So the reaction mixture was heated at 110°C for 24 hours. The product obtained was characterized on the basis of common spectroscopic methods as 2-chloro-4-(4-methoxyphenyl)-6-(4-methylphenyl)nicotinonitrile \(54a\), instead of the expected dihydropyridine \(53\) (Scheme 17).

![Scheme 17](image)

The product obtained was characterized on the basis of conventional spectroscopic methods. In the \(^1\)H NMR spectrum (Figure 1), \(54a\) showed singlets at \(\delta 2.43\) and \(\delta 3.89\) due to hydrogen atoms on the methyl and methoxy groups. The singlet at \(\delta 7.72\) indicated the presence of pyridinyl proton and all other aromatic protons were in accordance with the proposed structure. The methyl and methoxy carbon atoms on \(54a\) showed resonances at \(\delta 21.47\) and \(\delta 55.5\) respectively in the \(^13\)C NMR spectrum (Figure 2). The peak for nitrile carbon atom was present at \(\delta 114.64\) ppm. All other peaks at \(\delta 115.62, 118.15, 127.49, 127.75, 129.85, 129.99, 133.42, 141.68, 154.02, 156.04, 159.81, 161.5\) ppm due to aromatic carbon atoms confirmed the structure of the compound. In the IR spectrum (Figure 3), major peaks were present at 2841, 2222 (CN), 1583 and 819 cm\(^{-1}\). In the GCMS (Figure 4), the molecular ion
peak at m/z 334 and isotopic peak at m/z 336 also confirmed the compound as 2-chloro-4-(4-methoxyphenyl)-6-(4-methylphenyl)nicotinonitrile.

Figure 1 $^1$H NMR spectrum of 2-chloro-4-(4-methoxyphenyl)-6-(4-methylphenyl)nicotinonitrile 54a

Figure 2 $^{13}$C NMR spectrum of 2-chloro-4-(4-methoxyphenyl)-6-(4-methylphenyl)nicotinonitrile 54a
The mechanism of the reaction may be explained as follows. At first, chalcone is added to Vilsmeier-Haack reagent forming a dicationic intermediate 55, which facilitates the Michael reaction of dinitrile methylene anion to chalcone to get an adduct 56. The adduct 56 then underwent
sequential cyclization, chlorination and aromatization to afford 4,6-bis(phenyl)-2-chloronicotinonitrile 54a in good yields (Scheme 18).

Synthetic investigations on this particular reaction proved that 2-chloronicotinonitriles are formed only in the presence of Vilsmeier-Haack reaction conditions. However, a valuable observation that the Michael reaction of malononitrile to chalcones in the presence of POCl$_3$ leading to the formation of 4,6-bis(phenyl)-2-oxonicotinonitrile, was made in the meanwhile. Besides, the yield of the reaction was found to decrease at higher temperatures above 130$^\circ$C. The reaction was found to be general to other chalcones to afford functionalized nicotinonitriles in good yields (Scheme 19).
Table 1 Synthesis of 4,6-bis(aryl)-2-chloronicotinonitriles 54a-j

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<th>Ar&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Ar&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield (%)</th>
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4.3.2. Reactions of chalcones with malononitrile in the presence of POCl<sub>3</sub>: Synthesis of 4,6-bis(aryl)-2-oxonicotinonitriles 59a-f

In a pilot experiment, 1,3-bis(4-methoxyphenyl)-2-propen-1-one was treated with malononitrile in the presence of catalytic amount of phosphorous oxychloride at room temperature and then at a temperature of 110°C. The product obtained was characterized on the basis of common spectroscopic methods as 4,6-bis(4-methoxyphenyl)-2-oxonicotinonitrile 59a (yield, 50%). Later the yield of the reaction was improved by varying the amount of POCl<sub>3</sub> and it was observed that 4,6-bis(4-methoxyphenyl)-2-oxonicotinonitrile 59a can be obtained in 95% yield, when the reaction was conducted in the presence of equimolar amount of POCl<sub>3</sub> (Scheme 20).
In the $^1$H NMR spectrum (Figure 5), 59a showed two singlets of three protons at $\delta$ 3.83 and $\delta$ 3.86 corresponding to methoxy groups and a singlet of one proton at $\delta$ 8.12 due to the pyridone moiety. Other aromatic protons are present at $\delta$ 7.1 (d, 2H, $J = 8.8$ Hz), 7.16 (d, 2H, $J = 8.8$ Hz), 7.78 (d, 2H, $J = 8.8$ Hz) and 8.22 (d, 2H, $J = 8.8$ Hz) ppm. In the $^{13}$C NMR spectrum (Figure 6), the methoxy carbon appears at $\delta$ 55.44, the nitrile carbon at $\delta$ 114.31 and pyridone carbonyl group at 161.86 ppm. Other peaks are in accordance with the proposed structure. In the IR spectrum (Figure 7), a broad NH/OH peak, which is a characteristic feature of pyridone ring, is present. Besides, the nitrile group gave an absorption peak at m/z 2222 cm$^{-1}$ and carbonyl group at m/z 1608 cm$^{-1}$.

In GCMS (Figure 8), the peak appeared at m/z 331.

**Figure 5** $^1$H NMR spectrum of 4,6-bis(4-methoxyphenyl)-2-oxonicotinonitrile 59a
Figure 6 $^{13}$C NMR spectrum of 4,6-bis(4-methoxyphenyl)-2-oxonicotinonitrile 59a

Figure 7 IR Spectrum of 4,6-bis(4-methoxyphenyl)-2-oxonicotinonitrile 59a
The mechanism of the reaction may be explained as follows: Initially POCl$_3$ forms a complex with the chalcone 52, which facilitates the Michael addition of nucleophilic malononitrile at $\beta$-carbon atom of the chalcone. An intramolecular ring closure of 60, followed by the migration of POCl$_2$ to the nitrile group and aromatization of 63 result in the formation of intermediate 64, which on hydrolysis affords corresponding 2-pyridone 59 in good yields (Scheme 21).
The reaction was general to other substituted chalcones 52 to afford corresponding 2-pyridones 59a-f (Scheme 22).
Table 2 Synthesis of 4,6-bis(aryl)-2-oxonicotinonitriles 59a-f

<table>
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<td>f</td>
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Similar 2-pyridones are known in the literature from 1922 itself. Kohler et al have discussed the reactions of δ-ketonic nitriles and their further conversion to 2-pyridones under basic conditions. 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. Such compounds have found applications in the synthesis of some natural products like Nothapodytine B. Literature review revealed that 4,6-diaryl-2-oxonicotinonitriles are synthesized under simple base catalyzed conditions from chalcones or even from acetophenones and benzaldehydes. Still the new reaction is significant as it, being preceded in the presence of Lewis acids like phosphorous oxychloride, could be applied in the total synthesis of natural products with base sensitive functional groups.
4.3.3. Reactions of chalcones with Vilsmeier-Haack reagent: Synthesis of chlorovinyl amines 66a-e

Accidently, we noted that the yield of above reactions involving chalcone, malononitrile and the Vilsmeier-Haack reagent forming 2-chloropyridines is decreased at higher temperatures due to the formation of some unwanted by-products. Literature review showed that chalcones are reluctant to react with the Vilsmeier-Haack reagent under normal conditions. However, we observed that they are unreactive towards the Vilsmeier-Haack reagent even at higher temperatures of 100°C. 1,3-Diphenyl-2-propen-1-one 52b when treated with the Vilsmeier-Haack reagent at 130°C, N-[3-chloro-1,3-diphenyl-2-propenyl]-N,N-dimethylamine 66b was obtained in 76 % yield (Scheme 23).

![Scheme 23](image)

The identity of N-[3-chloro-1,3-diphenyl-2-propenyl]-N,N-dimethylamine 66b was proved on the basis of common spectroscopic methods. In the $^1$H NMR spectrum (Figure 9), the two methyl groups on the nitrogen atom were present at $\delta$ 3.02 and 3.18 as singlets. The CH proton adjacent to nitrogen was present at $\delta$ 4.78 as a doublet with $J = 8$ Hz and the vinylic proton at $\delta$ 6.82 as a doublet with $J = 8$ Hz. Other peaks were in accordance with the proposed structure. In the $^{13}$C NMR spectrum (Figure 10), the methyl carbons attached to nitrogen atom resonated at $\delta$ 35.34 and 39.57. The NCH carbon and vinylic carbon atoms resonated at 42.47 and 71.37 respectively. Other aromatic carbon atoms gave peaks at $\delta$ 126.76, 127.03, 128.35, 129.01, 129.24, 129.49, 129.52, 129.67 and 136.29 ppm. In the GCMS (Figure 11), the compound showed m/z = 271 corresponding to
molecular ion peak. In the IR spectrum major peaks were present at 2962, 2359, 1398 and 771 cm\(^{-1}\).

Figure 9 \(^1\)H NMR Spectrum of N-[3-chloro-1,3-diphenyl-2-propenyl]-N,N-dimethylamine 66b

Figure 10 \(^13\)C NMR spectrum of N-[3-chloro-1,3-diphenyl-2-propenyl]-N,N-dimethylamine 66b
Figure 11  GCMS of N-[3-chloro-1,3-diphenyl-2-propenyl]-N,N-dimethylamine 66b

The mechanism of the reaction is explained as follows: At a higher temperature DMF could either degrade to secondary amine and an aldehyde or to form Vilsmeier-Haack reagent in the presence of POCl₃. The chalcone undergo concerted dimethylamine promoted addition to Vilsmeier-Haack reagent to get an intermediate 71. Substitution of O-Vilsmeier reagent moiety by chlorine via an addition-elimination reaction resulted in the formation of N-[3-chloro-1,3-diphenyl-2-propenyl]-N,N-dimethylamine 66b (Scheme 24).
The reaction was general to all other chalcones 52 yielding corresponding chlorovinyl amines 66a-e (Scheme 25).
Table 3 Synthesis of N-[3-chloro-1,3-diphenyl-2-propenyl]-N,N-dimethylamines 66a-e

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4.4. Conclusion

In conclusion, we have investigated the reactions of chalcones with malononitrile in the presence of Vilsmeier-Haack reagent and POCl<sub>3</sub> leading to the synthesis of 4,6-bis(phenyl)-2-chloronicotinonitriles and 4,6-bis(phenyl)-2-oxonicotinonitriles. Moreover, chalcones underwent chloroamination under Vilsmeier-Haack reaction condition at higher temperature to afford chlorovinyl amines.

4.5. Experimental

Melting points were determined on a Büchi 530 melting point apparatus and were not corrected. The IR spectra were recorded from KBr pellets on a Shimadzu IR-470 spectrometer, and the frequencies are reported in cm<sup>-1</sup>. <sup>1</sup>H NMR spectra were recorded on a Bruker BIOSPIN (400 MHz) using TMS as internal standard and CDCl<sub>3</sub> and DMSO-d<sub>6</sub> as solvents. <sup>13</sup>C NMR spectra were recorded on a Bruker BIOSPIN (100 MHz) spectrometer using CDCl<sub>3</sub> and DMSO-d<sub>6</sub> as solvents. Electron impact mass spectra were obtained on a Finnigan-Mat 312 instrument or a Shimadzu model GCMS.
(Shimadzu QP-5000/5050A) instrument. All reagents were commercially available and were purified before use. Anhydrous Na$_2$SO$_4$ was used as drying agent.

4.5.1. Reactions of chalcones with malononitrile in the presence of Vilsmeier reagent: Synthesis of 4,6-bis(aryl)-2-chloronicotinonitriles 53a-j

**General Procedure**

The Vilsmeier-Haack reagent was prepared by mixing DMF (2 mL, 24 mmol) and POCl$_3$ (0.23 mL, 2.4 mmol) at 0°C followed by stirring at room temperature for 15 minutes. To the Vilsmeier-Haack reagent appropriate chalcone (2.5 mmol) and malononitrile (495 mg, 7.5 mmol) were added and the solution was stirred at 110°C for 24 hours. The reaction mixture was cooled, poured over ice-cold K$_2$CO$_3$ solution and extracted with diethyl ether (3 × 20 mL). The organic layer was washed with water, dried on anhydrous sodium sulfate and the solvent was removed by evaporation. The crude reaction mixture was purified by column chromatography (60-120 mesh) using hexane: ethyl acetate (90:10) solvent mixture as the eluent.

2-Chloro-4-(4-methoxyphenyl)-6-(4-methylphenyl)nicotinonitrile 54a was obtained from the reaction of 3-(4-methoxyphenyl)-1-(4-methylphenyl)-2-propen-1-one (630 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 194°C; yield 736 mg (88%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 2.43 (s, 3H), 3.89 (s, 3H), 7.07 (d, 2H, $J = 8.4$ Hz), 7.31 (d,
2H, J = 8 Hz), 7.62 (d, 2H, J = 8.4 Hz), 7.72 (s, 1H), 7.98 (d, 2H, J = 7.6 Hz) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$) = 21.47, 55.5, 106.03, 114.64, 115.62, 118.15, 127.49, 127.75, 129.85, 129.99, 133.42, 141.68, 154.02, 156.04, 159.81, 161.5 ppm.

GCMS m/z = 336 (M+2)$^+$, 334 (M$^+$).

IR (KBr) $\nu_{\text{max}}$ = 2841, 2222, 1583, 819 cm$^{-1}$.

2-Chloro-4,6-diphenylnicotinonitrile 54b

was obtained from the reaction of 1,3-diphenyl-2-propen-1-one (520 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 155°C; yield 610 mg (84 %).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.4 (t, 1H, J = 8.4 Hz), 7.48-7.523 (m, 4H), 7.56-7.59 (m, 3H), 8.006 (d, 1H, J = 12Hz), 8.013 (s, 1H), 8.028 (d, 1H, J = 12 Hz) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$) = 111.29, 115.99, 120.09, 126.54, 127.34, 128.0, 128.67, 128.92, 129.73, 133.93, 136.94, 141.03, 153.20, 160.25 ppm.

GCMS m/z = 292(M+2)$^+$, 290(M$^+$).

IR (KBr) $\nu_{\text{max}}$ = 2923, 2214, 1571, 698 cm$^{-1}$. 
2-Chloro-4-(4-methoxyphenyl)-6-phenylnicotinonitrile 54c was obtained from the reaction of 3-(4-Methoxyphenyl)-1-phenyl-2-propen-1-one (600 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 178°C; yield 711 mg (88%).

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 3.88\) (s, 3H), 7.09 (t, 1H, \(J = 9\) Hz), 7.27 (m, 2H), 7.45 (d, 1H, \(J = 3.6\) Hz), 7.52 (s, 1H), 7.64 (d, 2H, \(J = 8.4\) Hz), 7.78 (d, 1H, \(J = 8.8\) Hz), 8.081 (d, 2H, \(J = 9\) Hz) ppm.

\(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}) = 55.51, 106.47, 114.67, 118.59, 127.56, 128.42, 128.57, 129.10, 130.01, 130.24, 131.09, 136.21, 156.18, 159.81, 161.56 ppm.

GCMS m/z = 322 (M+2), 320 (M\(^+\)).

IR (KBr) \(\nu_{\text{max}} = 2959, 2224, 1581, 688\) cm\(^{-1}\).

2-Chloro-4-(4-chlorophenyl)-6-(4-methylphenyl)nicotinonitrile 54d was obtained from the reaction of 3-(4-chlorophenyl)-1-(4-methylphenyl)-2-propen-1-one (640 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 216-218°C; yield 736 mg (87%).

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 2.43\) (s, 3H), 6.84 (d, 1H, \(J = 7.6\) Hz), 7.32 (d, 2H, \(J = 8\) Hz),
7.467-7.55 (m, 4H), 7.594 (s, 1H), 7.965 (d, 1H, $J = 7.6$ Hz) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$) = 21.35, 119.76, 127.66, 128.28, 129.21, 129.52, 129.55, 129.68, 129.74, 130.09, 134.35, 135.84, 140.14, 148.66, 153.21 ppm.

GCMS m/z = 340(M+2)$^+$, 338(M$^+$).

IR (KBr) $\nu_{\text{max}}$ = 2208, 1579, 1497, 1286, 812 cm$^{-1}$.

2-Chloro-6-(4-chlorophenyl)-4-(4-methoxylphenyl)nicotinonitrile 54e was obtained from the reaction of 1-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-propen-1-one (680 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 238ºC; yield 788 mg (89 %).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.82 (s, 3H), 7.06 (d, 2H, $J = 7.6$ Hz), 7.47 (d, 2H, $J = 7.6$ Hz), 7.61 (d, 2H, $J = 8$ Hz), 7.71 (s, 1H), 8.02 (d, 2H, $J = 7.2$ Hz) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$) = 55.53, 113.2, 114.74, 115.37, 118.35, 127.48, 128.82, 129.38, 130.01, 134.62, 137.51, 154.5, 156.39, 158.49, 163.32 ppm.

GCMS m/z = 356(M+2)$^+$, 354(M$^+$).

IR (KBr) $\nu_{\text{max}}$ = 2222, 1582, 1186, 827 cm$^{-1}$. 

Mol. Wt.: 355.22
**2-Chloro-4,6-bis(4-chlorophenyl)nicotinonitrile 54f** was obtained from the reaction of 1,3-bis(4-chlorophenyl)-2-propen-1-one (690 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 238-240°C; yield 788 mg (88%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.40 (d, 1H, $J$ = 8.4 Hz), 7.49 (m, 2H), 7.58 (m, 3H), 7.72 (s, 1H), 7.96 (d, 1H, $J$ = 8.4 Hz), 8.04 (d, 1H, $J$ = 8.8 Hz) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$) = 107.04, 114.81, 128.72, 128.87, 129.46, 129.61, 129.73, 129.91, 137.20, 137.81, 143.83, 154.23, 155.48, 158.87 ppm.

GCMS m/z = 360(M+2)$^+$, 358(M$^+$).

IR (KBr) $\nu_{\text{max}}$ = 2924, 2224, 1582, 827 cm$^{-1}$.

**6-(4-Bromophenyl)-2-chloro-4-phenylnicotinonitrile 54g** was obtained from the reaction of 1-(4-bromophenyl)-3-phenyl-2-propen-1-one (720 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 180°C; yield 788 mg (85%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.41 (d, 1H, $J$ = 8 Hz), 7.55 (m, 2H), 7.63 (d, 4H, $J$ = 6.8 Hz),
2-Chloro-6-(4-methylphenyl)-4-phenylnicotinonitrile 54h was obtained from the reaction of 1-(4-methylphenyl)-3-phenyl-2-propen-1-one (560 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 165°C; yield 653 mg (85%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 2.27$ (s, 3H), 7.31 (d, 2H, $J = 7.2$ Hz), 7.38 (m, 2H), 7.48 (m, 3H), 7.83 (s, 1H), 7.94 (d, 1H, $J = 8$ Hz), 7.99 (d, 1H, $J = 7.6$ Hz) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$) = 21.69, 118.46, 122.03, 126.64, 127.32, 127.50, 128.27, 128.65, 128.93, 129.16, 129.33, 134.95, 135.58, 143.67, 144.42 ppm.

GCMS m/z = 306(M+2)$^+$, 304(M$^+$).

IR (KBr) $\nu_{\text{max}} = 2900, 2231, 1597, 825$ cm$^{-1}$.
2-Chloro-6-(4-chlorophenyl)-4-phenylnicotinonitrile 54i was obtained from the reaction of 1-(4-chlorophenyl)-3-phenyl-2-propen-1-one (610 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 234-236°C; yield 703 mg (86%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.26 (m, 2H), 7.487-7.637 (m, 5H), 7.76 (s, 1H), 8.05 (d, 2H, $J$ = 8 Hz) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$) = 114.5, 118.68, 128.38, 128.84, 129.26, 129.41, 130.66, 133.8, 135.2, 147.1, 152.7, 157.3, 160.1, 164.4 ppm.

GCMS m/z = 326(M+2)$^+$, 324(M$^+$).

IR (KBr) $\nu_{\text{max}}$ = 2231, 1585, 836 cm$^{-1}$.

2-Chloro-4,6-bis(4-methoxyphenyl)nicotinonitrile 54j was obtained from the reaction of 1,3-bis(4-methoxyphenyl)-2-propen-1-one (670 mg, 2.5 mmol) with malononitrile (495 mg, 7.5 mmol) under Vilsmeier-Haack condition as a pale yellow solid; mp 192-194°C; yield 788 mg (90%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.86 (s, 3H), 3.89 (s, 3H), 7.02 (d, 2H, $J$ = 8 Hz), 7.07 (d, 2H, $J$ = 8 Hz), 7.62 (d, 2H, $J$ = 8 Hz), 7.68 (s, 1H), 8.06 (d, 2H, $J$ = 8 Hz) ppm.
13C NMR (100 MHz, CDCl₃) = 55.49, 55.65, 114.45, 114.59, 117.55, 127.80, 128.61, 129.20, 129.95, 131.30, 134.50, 153.82, 155.91, 159.38, 161.42, 162.15 ppm.

GCMS m/z = 352(M+2)⁺, 350(M⁺).

IR (KBr) ν_max = 2222, 1597, 826 cm⁻¹.

4.5.2. Reactions of chalcones with malononitrile in the presence of POCl₃: Synthesis of 4,6-bis(phenyl)-2-oxonicotinonitrile 59a-f

General Procedure

A solution of appropriate chalcone (2.5 mmol), malononitrile (495 mg, 7.5 mmol) and POCl₃ (0.23 ml, 2.5 mmol) in toluene was heated at 110°C for 2 hours. The solvent was removed, reaction mixture was cooled and ice-cold water was added to the vessel. The precipitate was filtered, dried in a vacuum oven and recrystallized from methanol.

4,6-Bis(4-methoxyphenyl)-2-oxonicotinonitrile 59a was obtained from the reaction of 1,3-bis(4-methoxyphenyl)-2-propen-1-one (670 mg, 2.5 mmol) with malononitrile (165 mg, 2.5 mmol) in the presence of POCl₃ (0.23 ml, 2.5 mmol) using toluene as the solvent as a pale yellow colored solid; mp 226-228°C (reported mp 232–234°C)20; yield 788 mg (95 %).

1H NMR (400 MHz, DMSO-d₆) δ = 3.83 (s, 3H), 3.86 (s, 3H), 7.1 (d, 2H, J = 8.8
Hz), 7.164 (d, 2H, \(J = 8.8\) Hz), 7.78 (d, 2H, \(J = 8.8\) Hz), 8.12 (s, 1H), 8.22 (d, 2H, \(J = 8.8\) Hz) ppm.

\(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) = 55.44, 104.76, 114.31, 114.46, 115.74, 118.13, 127.32, 127.88, 129.42, 130.47, 152.45, 155.71, 158.58, 161.05, 161.86 ppm.

GCMS m/z = 331.

IR (KBr) \(\nu_{\text{max}}\) = 3367, 2222, 1656, 1608 cm\(^{-1}\).

4,6-Bis(4-methylphenyl)-2-oxonicotinonitrile 59b was obtained from the reaction of 1,3-bis(4-methylphenyl)-2-propen-1-one (590 mg, 2.5 mmol) with malononitrile (165 mg, 2.5 mmol) in the presence of POCl\(_3\) (0.23 ml, 2.5 mmol) using toluene as the solvent as a pale yellow colored solid; mp 288-290°C (reported mp 295–297°C\(^{20}\)), yield 697 mg (93 %).

4-(4-Chlorophenyl)-6-(4-methoxyphenyl)-2-oxonicotinonitrile 59c was obtained from the reaction of 3-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-propen-1-one (680 mg, 2.5 mmol) with malononitrile (165 mg, 2.5 mmol) in the presence of POCl\(_3\) (0.23 ml, 2.5 mmol)
using toluene as the solvent as a pale yellow colored solid; mp 272-274°C (reported mp 275–276°C)\textsuperscript{20}; yield 789 mg (94%).

\textbf{6-(4-Chlorophenyl)-4-phenyl-2-oxonicotinonitrile 59d} was obtained from the reaction of 1-(4-chlorophenyl)-3-phenyl-2-propen-1-one (610 mg, 2.5 mmol) with malononitrile (165 mg, 2.5 mmol) in the presence of POCl\textsubscript{3} (0.23 ml, 2.5 mmol) using toluene as the solvent as a pale yellow colored solid; mp 284-286°C (reported mp 284–286°C)\textsuperscript{20}; yield 694 mg (90%).

\textbf{6-(4-Bromophenyl)-4-(4-methylphenyl)-2-oxonicotinonitrile 59e} was obtained from the reaction of 1-(4-bromophenyl)-3-(4-methylphenyl)-2-propen-1-one (750 mg, 2.5 mmol) with malononitrile (165 mg, 2.5 mmol) in the presence of POCl\textsubscript{3} (0.23 ml, 2.5 mmol) using toluene as the solvent as a pale yellow colored solid; mp 290-292°C (reported mp 294–296°C)\textsuperscript{20}; yield 837 mg (92%).
6-(4-Methoxyphenyl)-4-phenyl-2-oxonicotononitile 59f was obtained from the reaction of with malononitrile (165 mg, 2.5 mmol) in the presence of POCl₃ (0.23 ml, 2.5 mmol) using toluene as the solvent as a pale yellow colored solid; mp 250-252°C (reported mp 255–257°C)²⁰; yield 700 mg (92%).

4.5.3. Reactions of chalcones with Vilsmeier-Haack reagent: Synthesis of chlorovinyl amines 66a-e

General Procedure

The Vilsmeier-Haack reagent was prepared by mixing DMF (2 mL, 24 mmol) and POCl₃ (0.23 mL, 2.4 mmol) at 0°C followed by stirring at room temperature for 15 minutes. To the Vilsmeier-Haack reagent appropriate chalcone (2.5 mmol) was added and the solution was heated at 130°C for 24 hours. The reaction mixture was cooled, poured over ice-cold K₂CO₃ solution and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with water, dried over anhydrous sodium sulfate and the solvent was removed by evaporation. The crude reaction mixture was purified by flash column chromatography on silica gel (100-200 mesh) using hexane: ethyl acetate (70:30) solvent mixture as the eluent.

N-[3-Chloro-3-(4-methoxyphenyl)-1-phenyl-2-propenyl]-N,N-dimethylamine 66a was obtained from the reaction of 1-(4-methoxyphenyl)-3-phenyl-2-propen-1-one (600 mg, 2.5 mmol) with the
Vilsmeier-Haack reagent prepared from DMF (2.9 ml, 37.5 mmol) and POCl₃ (0.34 ml, 3.75 mmol) at 130°C for 24 hours as a thick amber colored liquid; yield 600 mg (79%).

¹H NMR (400 MHz, CDCl₃) δ = 3.001 (s, 3H), 3.066 (s, 3H), 3.84 (s, 3H), 4.58 (d, 1H, J = 8.8 Hz), 6.54 (d, 1H, J = 9.2 Hz), 6.80-6.97 (m, 2H), 7.18-7.44 (m, 5H), 7.49-7.62 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃) = 42.75, 55.30, 55.45, 71.06, 113.66, 121.74, 128.35, 128.89, 129.09, 130.82, 130.92, 134.94, 144.04, 160.36 ppm.

GCMS m/z = 303(M+2⁺), 301(M⁺) (same as reported mass)²².

IR (film) νmax = 3400, 1512, 1252, 804 cm⁻¹.

N-[3-Chloro-1,3-diphenyl-2-propenyl]-N,N-dimethylamine 66b was obtained from the reaction of 1,3-diphenyl-2-propen-1-one (520 mg, 2.5 mmol) the Vilsmeier-Haack reagent prepared from DMF (2.9 ml, 37.5 mmol) and POCl₃ (0.34 ml, 3.75 mmol) at 130°C for 24 hours as a thick amber colored liquid; yield 516 mg (76%).
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 3.02\) (s, 3H), 3.18 (s, 3H), 4.78 (d, 1H, \(J = 8\) Hz), 6.82 (d, 1H, \(J = 8\) Hz), 7.30-7.61 (m, 8H), 7.67 (d, 2H, \(J = 8\) Hz) ppm.

\(^13\)C NMR (100 MHz, CDCl\(_3\)) = 35.34, 39.57, 42.47, 71.37, 126.76, 127.03, 128.35, 129.01, 129.24, 129.49, 129.52, 129.67, 136.29 ppm.

GCMS m/z = 273(M+2), 271(M+).

IR (film) \(\nu_{\text{max}} = 2962, 2359, 1398, 771\) cm\(^{-1}\).

N-[3-Chloro-1-(4-methoxyphenyl)-3-(4-methylphenyl)-2-propenyl]-N,N-dimethylamine 66c was obtained from the reaction of 3-(4-methoxyphenyl)-1-(4-methylphenyl)-2-propen-1-one (630 mg, 2.5 mmol) with the Vilsmeier-Haack reagent prepared from DMF (2.9 ml, 37.5 mmol) and POCl\(_3\)(0.34 ml, 3.75 mmol) at 130\(^\circ\)C for 24 hours as a thick amber colored liquid; yield 678 mg (86\%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 2.40\) (s, 3H), 3.27 (s, 3H), 3.34 (s, 3H), 3.72 (d, 1H, \(J = 6\) Hz), 3.87 (s, 3H), 5.54 (d, 1H, \(J = 8\) Hz), 6.81-6.89 (m, 2H), 7.09-7.39 (m, 4H), 7.441-7.458 (d, 2H, \(J = 6.8\) Hz) ppm.

\(^13\)C NMR (100 MHz, CDCl\(_3\)) = 21.46, 38.33, 40.11, 47.77, 55.50, 114.42, 115.47,
N-[3-Chloro-1-(4-chlorophenyl)-3-(4-methylphenyl)-2-propenyl]-N,N-dimethylamine 66d was obtained from the reaction of 3-(4-chlorophenyl)-1-(4-methylphenyl)-2-propen-1-one (640 mg, 2.5 mmol) with the Vilsmeier-Haack reagent prepared from DMF (2.9 ml, 37.5 mmol) and POCl$_3$(0.34 ml, 3.75 mmol) at 130°C for 24 hours as a thick amber colored liquid; yield 663 mg (83 %).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 2.26 (s, 3H), 3.19 (s, 3H), 3.32 (s, 3H), 4.12 (d, 1H, $J$ = 6.8 Hz), 6.28 (d, 1H, $J$ = 7.2 Hz), 7.27-7.45 (m, 4H), 7.487-7.506 (d, 2H, $J$ = 7.6 Hz), 7.53-7.66 (m, 2H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$) = 21.52, 41.10, 43.00, 60.45, 106.18, 127.04, 127.56, 129.39, 129.44, 130.31, 134.26, 137.19, 142.94, 151.11 ppm.

GCMS m/z = 321(M+2)$^+$, 319(M$^+$).

IR (film) $\nu_{\text{max}}$ = 2935, 1239, 1102, 813 cm$^{-1}$. 

117.42, 127.04, 129.06, 129.66, 129.83, 139.52, 143.77, 158.19 ppm. 

GCMS m/z = 317(M+2)$^+$, 315(M$^+$).

IR (film) $\nu_{\text{max}}$ = 2923, 1240, 1171, 536 cm$^{-1}$. 

$\text{C}_{18}\text{H}_{19}\text{Cl}_2\text{N}$

Mol. Wt.: 320.26
N-[3-Chloro-3-(4-methylphenyl)-1-phenyl-2-propenyl]-N,N-dimethylamine 66e was obtained from the reaction of 1-(4-methylphenyl)-3-phenyl-2-propen-1-one (560 mg, 2.5 mmol) with the Vilsmeier-Haack reagent prepared from DMF (2.9 ml, 37.5 mmol) and POCl₃ (0.34 ml, 3.75 mmol) at 130°C for 24 hours as a thick amber colored liquid; yield 562 mg (78%).

\[^1\text{H}\text{ NMR (400 MHz, CDCl}_3\text{)}\] \(\delta = 2.32\) (s, 3H), 2.93 (s, 3H), 3.09 (s, 3H), 4.50 (d, 1H, \(J = 9.2\) Hz), 6.48 (d, 1H, \(J = 9.2\) Hz), 7.12 (d, 2H, \(J = 7.6\) Hz), 7.248-7.388 (m, 5H), 7.441-7.536 (m, 2H) ppm.

\[^{13}\text{C}\text{ NMR (100 MHz, CDCl}_3\text{)} = 21.12, 41.66, 43.24, 70.73, 110.71, 126.43, 127.01, 128.61, 128.81, 129.79, 134.55, 134.79, 139.03, 142.18\) ppm.

GCMS \(m/z = 287(M+2)^+\), 285 (\(M^+\)).

IR (film) \(\nu_{\text{max}} = 2935, 1251, 767, 514\) cm\(^{-1}\).
4.6. References


