Chapter 3
Chloromethyleneiminium Salt Mediated Three-component Reactions for the Synthesis of Nicotinonitriles

3.1. Introduction

The Vilsmeier–Haack reaction has emerged as a popular tool for the formylation and acylation of a large number of aromatic and heteroaromatic compounds.\(^1\) Appropriately substituted alkenes, alcohols, acetals, ketals, dithioketals and ketene dithioacetals undergo a variety of transformations on treatment with the Vilsmeier–Haack reagent.\(^2\) Typically the reactions of active methylene compounds with reagents of the Vilsmeier type afford β-chloromethyleneiminium salts or β-chlorovinyl aldehydes,\(^3\) which have been recognized as useful intermediates in heterocyclic synthesis especially in the synthesis of pyridine derivatives. The interception of malononitrile with functionalized chloromethyleneiminium salt formed from aroylketene dithioacetals 1, leading to the synthesis of 5-aryl-2-chloro-6-(methylsulfanylnicotinonitriles 5, reported by Asokan et al. in 2006, explored new possibilities of Vilsmeier-Haack reagent in three component reactions (Scheme 1).\(^4\)
As a continuation to these studies, acetophenones and other ketones were treated with malononitrile under Vilsmeier–Haack condition and the results of our investigations are presented in this chapter.

3.2. Synthesis of Pyridines

Pyridine and fused pyridine moieties are present in numerous natural products such as quinoline and isoquinoline alkaloids and nicotine and its analogues. Due to their antiviral and antibacterial activities they are of interest as antitumour and anti-inflammatory agents. Some polysubstituted pyridines are used as non-linear optical materials, electrical materials, chelating agents in metal-ligand chemistry and fluorescent liquid crystals. As pyridine derivatives have distinct properties of interest, continuous synthetic efforts have been devoted to the development of reactions leading to their formation. Our research group had the interest of synthesizing differently substituted pyridines from functionalized chloromethyleneiminium salt intermediate. So in this section we have discussed important reactions involving chloromethyleneiminium salt or their synthetic equivalents for the synthesis of pyridines and their derivatives. Besides, a few multicomponent reactions leading to the synthesis of pyridines also have been described in this section.

3.2.1. Chloromethyleneiminium salt mediated synthesis of pyridines

Synthetic investigations on iminoalkylation and multiple iminoalkylations have led to the development of new strategies for the synthesis of functionalized pyridines and their derivatives. The Vilsmeier-Haack reactions of simple alkenes possessing alkyl substituents are rather complex due to subsequent iminoalkylations and migrations of carbon-
carbon bonds. For example, simple alkenes like isobutene 6 on reaction with Vilsmeier-Haack reagent affords 2,7-naphthyridine aldehyde 8 via a multiple iminoalkylated intermediate 7 (Scheme 2).\textsuperscript{11}

![Scheme 2](image)

On extending the reaction to 2-phenylpropene 9, nicotinaldehydes 10 were formed in good yields (Scheme 3).

![Scheme 3](image)

It is interesting to note that the multiple iminoalkylation of simple alkenes are controlled by substituents on the allylic carbon atoms. For example, the Vilsmeier-Haack reaction of camphene 11 affords simple formylated product 12 (Scheme 4) while that of methylenebornane 13 undergoes multiple iminoalkylations to afford pyridine derivatives 15 (Scheme 5).\textsuperscript{12}

![Scheme 4](image)
In the course of our studies directed towards the utilization of chloromethyleneiminium salts in the synthesis of heterocyclic compounds, we have developed convenient methods for the synthesis of substituted pyridines and naphthyridines. For example carbinols 16 derived from acetophenones undergo multiple iminoalkylation reaction followed by reaction with ammonium acetate to afford substituted pyridines 17 (Scheme 6). In this reaction the iminoalkylation is considered to occur on an alkene intermediate.

When the same protocol was extended to aliphatic or alicyclic carbinols 18, [2,7]naphthyridine derivatives 19 were obtained (Scheme 7).

Koyama et al reported the synthesis of thienopyridine derivative 22 from 3-cyanomethylthiophene 20 via an intermediate iminium salt 21 (Scheme 8).
It is interesting to note that the Vilsmeier-Haack reaction of malononitrile 3 affords simple nicotinonitrile derivative 24 via an intermediate 23 (scheme 9).\textsuperscript{15}

Recent studies on the applications of iminoalkylated intermediates have resulted in many heterocyclic syntheses. For example, 2-chloronicotinonitriles 27 and fused bicyclo-2-chloro-3-cyanopyridine 29 are obtained from alkylidene malononitriles 25 and 28 respectively by the Vilsmeier reaction (Scheme 10 and 11).\textsuperscript{16} In these reactions the iminoalkylated intermediates undergo cyclization reaction to afford the corresponding nicotinonitriles.

Similar approach to synthesize fused tricyclo-2-chloro-3-cyanopyridine 31 from $\alpha$-tetralone, has been reported by Aadil et al (Scheme 12).\textsuperscript{17}
The Vilsmeier cyclization of 2'-aminochalcones 32 provides a mild one-pot synthesis of 2-aryl-4-chloro-N-formyl-1,2-dihydroquinolines 33 (Scheme 13). The scope of the reaction has been extended for the synthesis of quinolines themselves, by replacing 2'-aminochalcones with 2'-azidochalcones as the starting material.

\[ \text{Scheme 13} \]

\[ \text{o-Aminoacetophenones 34 react with the Vilsmeier-Haack reagent to afford the corresponding 4-chloroquinoline derivatives 35 (Scheme 14).}^{19} \]

\[ \text{Scheme 14} \]

Vilsmeier–Haack reaction of arylacetones 36 leads to the formation of conjugated iminium salts which on ammonium acetate induced cyclization afford 5-aryl-4-chloronicotinaldehyde 37 in good yields (Scheme 15).^{20}
Benzyl ethyl ketone 38 or dibenzyl ketone under similar conditions gave 4-chloro-3-methyl-5-phenylpyridine 39 (Scheme 16).

![Scheme 16](image)

Vilsmeier-Haack reaction of benzimidazole derivatives 40 lead to the synthesis of benzimidazo[1,2-b]isoquinoline derivatives 41 instead of the expected acenaphththalene derivatives (Scheme 17).²¹

![Scheme 17](image)

The dienamine 42 affords the corresponding iminium salts 43 resulting from disubstitution in the presence of Vilsmeier-Haack reagent. The iminium salt 43 on treatment with aqueous ammonium chloride solution affords pyridine-3-carbaldehyde 44 (Scheme 18).²²

![Scheme 18](image)

Several enamides have been used as precursors for the synthesis of pyridone derivatives. The enamides 45 on reaction with iminium salt afford
N-substituted 2-pyridone derivatives 46 and pyridine-3-carbaldehyde derivative 47 in 14-69% yield (Scheme 19).^{23}

Scheme 19

A convenient iminium salt mediated synthesis of 2-pyridone derivative 49 was achieved by the Vilsmeier-Haack formylation followed by cyclization of the acylenamine 48 (Scheme 20).^{24}

Scheme 20

In the literature there are a number of reports on the synthesis of quinolines and their derivatives using the chloromethyleneiminium salts prepared from anilides.^{25} The Vilsmeier-Haack reaction of acylanilides 50 afforded the functionalized quinoline 52 in good yields (Scheme 21).^{26}

Scheme 21

In the case of N-phenylacetanilide 53 Vilsmeier-Haack reaction afforded 1-phenyl-2-quinolones 55 (Scheme 22).^{27}
Similarly N-acetylhomocysteine thiolactone 56 gives 5-chloro-3-formylthieno[2,3-b]pyridine 57 (Scheme 23).\(^{28}\)

Recent studies from this laboratory found that the Vilsmeier-Haack reaction of \(\alpha\)-hydroxyketene dithioacetals 58, followed by quenching with ammonium acetate, leads to 2-methylsulfanyl-4-phenylpyridine 59 (Scheme 24).\(^{29}\)

Vilsmeier-Haack reaction of acylketene dithioacetals 60, derived from phenylacetone afforded 4-chloro-2-(methylsulfanyl)-3-phenylpyridines 62 in good yield (Scheme 25).
The doubly activated ketene dithioacetals undergo an addition elimination sequence with primary and secondary amines to yield the corresponding N,S-acetals and N,N-acetals in high yields. Junjappa et al have studied the reactivities of various α-oxoketene-N,S-acetals 63 with the Vilsmeier-Haack reagent to afford functionalized quinolines 64 in good yields (Scheme 26).\(^{30}\)

![Scheme 26](image)

The use of multicomponent transformations or domino reactions is a very efficient strategy for the production of compound ensembles of high diversity required in modern search for desired structures. A typical example for such a reaction for the synthesis of substituted pyridines via a chloromethyleneiminium salt intermediate has been reported from our laboratory (Scheme 1).\(^4\) Similar reactions leading to the synthesis of pyridines from simple molecules are described in the following section.

### 3.2.2. Multicomponent reactions for the synthesis of pyridines

The production of dihydropyrimidinones via the Biginelli reaction certainly ranks as one of the most recognized and often used MCRs for the generation of novel pyrimidine scaffolds. InCl\(_3\) mediated one-pot synthesis of indol-3-yl pyridine 67 through multicomponent reaction have been described recently (Scheme 27).\(^{31}\)

![Scheme 27](image)
Substituted benzaldehydes 68 are known to condense with two molecules of malononitrile 3 in the presence of pyrrolidine 69 to afford 2-amino-4-aryl-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile 70 in moderate yields (Scheme 28). In these reactions morpholine substituted nicotinonitriles are prepared using morpholine instead of pyrrolidine.

![Scheme 28](image)

In the literature there are some reports on the reactions of chalcones with cyanomethylene compounds leading to the formation of nicotinonitriles. Raghukumar et al have synthesized 4,6-diaryl-2-(pyrrolidin-1-yl) nicotinonitriles 72 in a one-pot method from 1,3-diaryl-prop-2-en-1-ones 71 and malononitrile 3 in the presence of pyrrolidine 69 in 44% yield (Scheme 29). In this reaction along with 72, 3-amino-2,4-dicyano-5-(2-thienyl)biphenyls 73 also were obtained.

![Scheme 29](image)

A multicomponent reaction of aldehyde 74, malononitrile and 5-amino-3-methyl-1-phenylpyrazole 75 was carried out smoothly in [bmim][BF4] without any added catalyst. Through this reaction, pyrazolo[3,4-b]pyridines 76 were obtained conveniently and in a controlled manner at different temperatures (Scheme 30).
Scheme 30

Substituted pyridines 80 can be synthesized in moderate to good yields in a consecutive one-pot, four-component process by a coupling–isomerization–enamine addition–cyclocondensation sequence of an electron poor (hetero) aryl halide 77, a terminal propargyl alcohol 78, an enamine 79, and ammonium chloride (Scheme 31).35

Scheme 31

The reaction of N-silylated iminoethers 81 with 2-substituted acetyl chlorides 82 yields activated 2-azadienes. They were shown to react with electron deficient acetylenic dienophiles 83 to yield pyridones 84 (Scheme 32).36

Scheme 32

A series of new polycyclic-fused isoxazolo[5,4-b]pyridines 87 and 89 were obtained by a one-pot tandem reaction under microwave irradiation in
water (Scheme 33 and 34). Without any use of additional reagent or catalyst, the synthetic protocol represents a green one and makes this methodology suitable for library synthesis in drug discovery efforts.\(^{37}\)

![Scheme 33](image1)

A variety of 1,2,3,4-tetrahydroquinolines 93 can be prepared by a new three component condensation of an imine 90, an \(\alpha\)-branched and enolizable aldehyde 91 and a nucleophile, under ytterbium(III)trifluoromethane sulfonate [Yb(OTf)\(_3\)] catalysis (Scheme 35).\(^{38}\)

![Scheme 34](image2)

A three-component cyclocondensation of methyl 2-oxo-4-(trimethylsilyl)but-3-ynoate and N-[3-oxo-3-(oxazol-4-yl)propanoyl]serine 94 for the synthesis of 2,3,6- trisubstituted pyridine 96 was achieved by following a Bohlmann-Rahtz heteroannulation in the presence of ammonium acetate in ethanol (Scheme 36).\(^{39}\)
Scheme 36

Highly chemo and regioselective synthesis of polysubstituted pyridines 99 and isoquinolines have been reported by the multicomponent reaction of arynes 97, isocyanides, and terminal alkynes 98 (Scheme 37).\(^\text{40}\)

![Diagram of Scheme 36]

Scheme 37

A number of 3-aminoimidazo[1,2-a]pyridines 102 were synthesized in the presence of tin (II) chloride dihydrate as a catalyst to promote the three-component Groebke condensation reaction from a variety of aromatic aldehydes 68, 2-aminopyridines 100, and isonitriles 101 at room temperature (Scheme 38).\(^\text{41}\)
Several new pyrazolo[3,4-b]pyridine derivatives 106 were synthesized by one-pot cyclocondensation of the components; 1,3-diphenyl-1H-pyrazol-5-amine 103, p-substituted benzyolacetonitriles 105 and an aldehyde 104. The condensations were most effective when ammonium acetate was used as the base catalyst (Scheme 39).42

Recently, we have shown that the Vilsmeier–Haack reagent can act as a Knoevenagel base/buffer for the synthesis of 5-aroyl-2-chloro-6-(methylsulfanyl)nicotinonitriles from α-oxoketene dithioacetals (Scheme 1).4 It was also noted that 6-aryl-2-chloronicotinonitriles 109 are formed from enaminketones 107 via a chlorosubstituted intermediate 108 (Scheme 40).43

We envisioned that this new three-component strategy would be applicable to simple enolizable ketones for the synthesis of a variety of pyridine derivatives. Our results, which are described in this chapter, demonstrate the Vilsmeier–Haack reaction as an example of a three-
component reaction for the synthesis of nicotinonitriles from acetophenones, α-tetralone and benzylidene acetones. This approach is novel in heterocyclic synthesis and should have wide applications in chloromethyleneiminium salt mediated annulation reactions.

3.3. Results and Discussion

3.3.1. Reactions of acetophenones with Vilsmeier-Haack reagent in the presence of malononitrile: Synthesis of 6-aryl-2-chloronicotinonitriles 117a-i

It is known in the literature that on treatment with the Vilsmeier–Haack reagent, enolizable carbonyl compounds undergo iminoalkylation to afford chloro-substituted vinamidinium salts, which could be exploited for the synthesis of substituted pyrroles and pyridines employing multistep reaction strategies. So it was justifiable to think that acetophenone would be a potential precursor for the synthesis of 6-aryl-2-chloronicotinonitriles as in the case of β-enaminoketones under Vilsmeier-Haack reaction conditions (Scheme 41).

![Scheme 41](attachment:image.png)

In a pilot experiment, simple acetophenone 115a was treated with 1.5 equivalent of malononitrile under Vilsmeier-Haack reaction condition. The reaction mixture on aqueous work up using saturated potassium
carbonate solution afforded 2-chloro-6-phenylnicotinonitrile **117a** in good yield (Scheme 42).

![Scheme 42](image)

Literature survey showed that 2-chloro-6-phenylnicotinonitrile is an important substrate for the synthesis of natural products such as vitamins. The product was characterized on the basis of common spectroscopic methods. The $^1$H NMR spectrum (Figure 1) of 2-chloro-6-phenylnicotinonitrile **117a** showed two doublets with coupling constant 11.4 Hz, one at $\delta$ 7.29 and the other at $\delta$ 8.06, for H-4 and H-5 protons of the pyridine ring. The other peaks present in the spectrum were a doublet of coupling constant 8 Hz for two protons at $\delta$ 7.79 and a multiplet of three protons at $\delta$ 7.46-7.54 for aromatic protons. The $^{13}$C NMR spectrum (Figure 2) showed resonances at $\delta$ 111.4, 113.2, 119.3, 127.7, 129.0, 129.3, 131.8, 132.4, 134.9, 151.0, 154.6 and 154.9 ppm. The IR spectrum (Figure 3) of the compound showed aromatic stretching at 3040 cm$^{-1}$, CN stretching at 2219.91 cm$^{-1}$, C=C stretching at 1568 cm$^{-1}$ and other major absorptions at 1342.4, 914.2, 761.8 and 682.1 cm$^{-1}$. The EIMS spectrum (Figure 4) of the compound showed molecular ion peak at m/z 214 and 216 (3:1) for M$^+$ and (M+2)$^+$ peaks respectively. In 1998, Cyranski *et al* reported crystallographic studies on this substance and showed that the molecule was not planar and hence the symmetry of the molecule is lost.
Figure 1 $^1$H NMR Spectrum of 2-chloro-6-phenylnicotinonitrile 117a

Figure 2 $^{13}$C NMR Spectrum of 2-chloro-6-phenylnicotinonitrile 117a
Figure 3 IR Spectrum of 2-chloro-6-phenylnicotinonitrile 117a

Figure 4 EIMS of 2-chloro-6-phenylnicotinonitrile 117a
The mechanism for the formation of 2-chloro-6-phenylnicotinonitrile can be explained by the well known Vilsmeier–Haack reaction of acetophenones followed by addition of malononitrile to the resulting chlorovinamidinium salt 118 and cycloaromatization of the adduct 119 (Scheme 43). Apparently, under Vilsmeier-Haack reaction condition functionalized chlorovinamidinium salt 118 was formed from acetophenone. The addition of malononitrile to vinamidinium salt resulted in the formation of 119, which on cycloaromatization with the elimination of dimethylamine afforded 2-chloro-6-phenylnicotinonitrile 117a.

![Scheme 43](image)

Other substituted enolizable ketones 115a-i also gave corresponding 6-aryl-2-chloronicotinonitriles 117a-i in good yields and they were characterized on the basis of IR, ¹H NMR, ¹³C NMR and EIMS/GCMS spectral data (Scheme 44).

![Scheme 44](image)
### Table 1 Synthesis of 6-aryl-2-chloronicotinonitriles 117a-i

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### 3.3.2. Reaction of α-tetralone with Vilsmeier-Haack reagent in the presence of malononitrile: Synthesis of 2-chloro-5,6-dihydrobenzo[h]quinoline-3-carbonitrile 122

In the literature, there are only a few reports on the synthesis of dihydrobenzoquinoline. Ramendra et al have put forward a non-catalytic approach to the synthesis of 5,6-dihydrobenzo[h]quinolines.⁴⁸ 2-Amino-4-(4-chlorophenyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile is a phenantridine analogue which shows strong fluorescent properties.⁴⁹ Kumar et al have reported the preparation of some dihydrodiols and diolepoxides from
tetrahydrobenzo[f]quinolines.\textsuperscript{50} Synthesis of novel benzochromene, benzoquinoline, benzochromenopyrimidine and pyrimidobenzoquinoline derivatives have also been put forward.\textsuperscript{51} A new product, namely, 2-methyl-3-ethyl methanoate benzo[h]quinoline was synthesized from an arylenamine using Vilsmeier reagent. The product was identified by classical and usual spectroscopic techniques as well as X-ray structure determination and a detailed potential scheme reaction way was proposed.\textsuperscript{52} \(\beta\)-Oxoacid esters in the synthesis of benzo[f]quinoline derivatives have been described.\textsuperscript{53} Synthesis of some new S-substituted thio- and thieno[2,3-b]benzo[h]quinoline derivatives have also been put forward.\textsuperscript{54}

On extending the above strategy to \(\alpha\)-tetralone, 2-chloro-5,6-dihydrobenzo[h]quinoline-3-carbonitrile \textbf{122} was obtained in 87 % yield (Scheme 45).

\begin{equation}
\begin{array}{c}
\text{121} \\
\text{O} \\
\text{NC}</array> \xrightarrow{\text{POCl}_3, \text{DMF}} \begin{array}{c}
\text{122} \\
\text{Cl} \\
\text{N} \\
\text{CN}
\end{array}
\end{equation}

\textbf{Scheme 45}

The identity of 2-chloro-5,6-dihydrobenzo[h]quinoline-3-carbonitrile \textbf{122} was proved on the basis of common spectroscopic methods. In the \(^1\text{H}\) NMR spectrum (Figure 5), the compound showed two triplets at \(\delta\) 2.96 and \(\delta\) 3.05 due to methylene protons and a singlet at \(\delta\) 8.21 due to heterocyclic H-4 proton. In the \(^{13}\text{C}\) NMR spectrum (Figure 6), the methylene carbon atoms resonated at \(\delta\) 25.2 and \(\delta\) 26.9, the nitrile carbon atom at \(\delta\) 114.4 and other ring carbon atoms at \(\delta\) 82.3, 112.6, 127.4, 127.8, 128.9, 131.3, 132, 138.3, 144.9, 155.4 ppm. In the mass spectrum, the compound showed molecular ion peak at m/z 240 and isotopic peak at m/z 242. In the IR spectrum, the compound showed major peaks at 2214 cm\(^{-1}\) and 1524 cm\(^{-1}\).
Figure 5 $^1$H NMR Spectrum of 2-chloro-5,6-dihydrobenzo[h]quinoline-3-carbonitrile 122

Figure 6 $^{13}$C NMR Spectrum of 2-chloro-5,6-dihydrobenzo[h]quinoline-3-carbonitrile 122
3.3.3. Reaction of benzylidene acetones with Vilsmeier-Haack reagent in the presence of malononitrile: Synthesis of 2-chloro-6-[(E)-2-phenylethenyl]pyridine-3-carbonitriles 124a-c

It is interesting to note that functionalized ketones such as benzylidene acetones 123a-c also react under these conditions to give the corresponding chloropyridines 124a-c (Scheme 46).

![Scheme 46]

Table 2 Synthesis of 2-chloro-6-[(E)-2-phenylethenyl]pyridine-3-carbonitriles 124a-c

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<th>Yield (%)</th>
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<tr>
<td>b</td>
<td>Cl</td>
<td>58</td>
</tr>
<tr>
<td>c</td>
<td>OCH₃</td>
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</table>

All the arylethenylnicotinonitriles 124a-c were characterized on the basis of common spectroscopic methods. In the ¹H NMR spectrum (Figure 7), the representative compound 124a, 2-chloro-6-(2-phenylethenyl)pyridine-3-carbonitrile showed peaks at δ 6.93 (d, 1H, J = 12 Hz, H-5) and δ 8.02 (d, 1H, J = 12 Hz, H-4) due to heterocyclic protons. The doublet at δ 7.04 with coupling constant J = 15 Hz and an extra proton in the aromatic region indicated the presence of trans-alkenyl protons present in the molecule. In the ¹³C NMR spectrum (Figure 8), the nitrile carbon atom is present at δ 113.5 and the methene carbon atoms on the arylethenyl moiety are present at δ 111.7 and δ 142.5. Other aromatic carbon atoms are in accordance with the proposed structure. In the FABMS, 124a showed molecular ion peak at m/z 240 and isotopic peak at m/z 242. In the IR spectrum, the nitrile group gave an absorption peak at 2220 cm⁻¹ and other major peaks at 1562, 1199, 1146 and 957 cm⁻¹.
Figure 7  $^1$H NMR Spectrum of 2-chloro-6-[(E)-2-phenylethenyl]pyridine-3-carbonitrile 124a

Figure 8  $^{13}$C NMR Spectrum of 2-chloro-6-[(E)-2-phenylethenyl]pyridine-3-carbonitrile 124a
3.4. Conclusion

In conclusion, simple enolizable ketones undergo one-pot iminoalkylation followed by sequential condensation with malononitrile, cyclization and aromatization under Vilsmeier–Haack reaction conditions to afford 2-chloronicotinonitriles. This methodology opens a new route to a one-pot multicomponent reaction under Vilsmeier–Haack reaction conditions.

3.5. 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\(^{-1}\). \(^1\)H NMR spectra were recorded on a Bruker WM 300 (300 MHz) and Bruker BIOSPIN (400 MHz) spectrometer using TMS as internal standard and CDCl\(_3\) as solvent. \(^13\)C NMR spectra were recorded on a Bruker WM 300 (75.47 MHz) and Bruker BIOSPIN (100 MHz) spectrometer using TMS as internal standard and CDCl\(_3\) as solvent. 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.

3.5.1. Reactions of acetophenones with Vilsmeier-Haack reagent in the presence of malononitrile: Synthesis of 6-aryl-2-chloronicotinonitriles 117a-i

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 arylketone (1 mmol) was added and the solution was stirred at room temperature for 12 hours. To this malononitrile (1g, 1.5 mmol) was added and the reaction mixture was further heated at 90°C for 2 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 (97:3) solvent mixture as the eluent.

2-Chloro-6-phenynicotinonitrile 117a was obtained by the reaction of acetophenone 115a (120 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow crystalline solid; mp 112-114°C; yield 112 mg (52%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.29 (d, 1H, $J$ = 11.4 Hz, H-5), 7.46-7.54 (m, 3H, ArH), 7.79 (d, 2H, $J$ = 8Hz, ArH), 8.06 (d, 1H, $J$ = 11.4 Hz, H-4) ppm.

$^{13}$C NMR (75.47 MHz, CDCl$_3$) $\delta$ = 111.4, 113.2, 119.3, 127.7, 129.0, 129.3, 131.8, 132.4, 134.9, 151.0, 154.6, 154.9 ppm.

EIMS m/z (%) = 216 [(M+2)$^+$, 11], 214 (M$^+$, 27), 180 (18), 179 (100), 153 (12), 152 (59), 127 (5), 125 (23), 105 (4), 99 (11), 77 (22).

IR (KBr) $\nu_{\text{max}}$ = 3040, 2220, 1568, 1342, 914 cm$^{-1}$.

2-Chloro-6-(4-methylphenyl)nicotinonitrile 117b was obtained by the reaction of 1-(4-methylphenyl)-1-ethanone 115b (134 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow colored crystals; mp 140-142°C; yield 147 mg (64%).
$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.5$ (s, 3H, CH$_3$), 7.26-7.30 (m, 3H, Ar and H-5), 7.70 (d, 2H, $J = 8$ Hz, Ar), 8.04 (d, 1H, $J = 12$ Hz, H-4) ppm.

$^{13}$C NMR (75.47 MHz, CDCl$_3$): $\delta = 21.44$, 84.6, 111.58, 113.3, 118.5, 127.8, 129.8, 132.3, 143.7, 151.3, 154.7 ppm.

GCMS m/z = 230 (M+2$^+$), 228 (M$^+$).

IR (KBr) $\nu_{\text{max}} = 2922, 2220, 1570, 1342, 1202, 916$ cm$^{-1}$.

2-Chloro-6-(4-methoxyphenyl)nicotinonitrile 117c was obtained by the reaction of 1-(4-methoxyphenyl)-1-ethanone 115c (150 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow crystalline solid; mp 160-162°C; yield 108 mg (44%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta = 3.9$ (s, 3H, OCH$_3$), 6.99 (d, 2H, $J = 8$ Hz, ArH), 7.25 (d, 1H, $J = 11.4$ Hz, H-4), 7.79 (d, 2H, $J = 8Hz$, ArH), 8.05 (d, 1H, $J = 11.4$ Hz, H-4) ppm.

$^{13}$C NMR (75.47 MHz, CDCl$_3$) $\delta = 55.65$, 111.88, 113.64, 114.54, 117.23, 127.25, 129.82, 137.20, 151.02, 155.10, 163.37 ppm.

EIMS m/z (%) = 246 [(M+2$^+$), 16], 244 (M$^+$, 63), 230 (20), 218 (52), 209 (100), 194 (35), 183 (7), 149 (88), 139 (51), 97 (91).

IR (KBr) $\nu_{\text{max}} = 2942, 2224, 1562, 1352, 1009, 560.0$ cm$^{-1}$. 

C$_{13}$H$_{9}$ClN$_2$O  
Mol. Wt.: 244.68
2-Chloro-6-(4-chlorophenyl)nicotinonitrile 117d

was obtained by the reaction of 1-(4-chlorophenyl)-1-ethanone 115d (155 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow colored crystals; mp 158-160°C; yield 129 mg (52%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.27$ (d, 1H, $J = 12$ Hz, H-5), 7.47 (d, 2H, $J = 9$ Hz, Ar), 7.74 (d, 2H, $J = 9$ Hz, Ar), 8.06 (d, 1H, $J = 12$ Hz, H-4) ppm.

$^{13}$C NMR (75.47 MHz, CDCl$_3$): 85.89, 111.39, 113.1, 119.6, 128.93, 129.38, 133.44, 138.95, 149.54, 154.34 ppm.

GCMS m/z = 250 (M+2)$^+$, 248 (M$^+$).

IR (KBr) $\nu_{max} = 3040, 2228, 1575, 1406, 912$ cm$^{-1}$.

6-(4-Bromophenyl)-2-chloronicotinonitrile 117e

was obtained by the reaction of 1-(4-bromophenyl)-1-ethanone 115e (199 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow colored crystals; mp 158-160°C; yield 109 mg (37%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.28$ (d, 1H, $J = 12$ Hz, H-5), 7.61-7.69 (m, 4H, Ar), 8.05 (d, 1H, $J = 12$ Hz, H-4) ppm.

$^{13}$C NMR (75.47 MHz, CDCl$_3$): 85.9, 111.38, 113.1, 119.6, 127.4, 129, 132.33, 133.85, 149.62, 154.31 ppm.

GCMS m/z = 294(M+2)$^+$, 292 (M$^+$).

IR (KBr) $\nu_{max} = 2222, 1570, 1393, 825$ cm$^{-1}$.
2-Chloro-6-(3-methoxyphenyl)nicotinonitrile 117f was obtained by the reaction of 1-(3-methoxyphenyl)-1-ethanone 115f (150 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow colored crystals; mp 144-146°C; yield 120 mg (49%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 3.8$ (s, 3H, OCH$_3$), 6.95 (d, 2H, $J = 8$ Hz, ArH), 7.25 (d, 1H, $J = 11.4$ Hz, H-4), 7.79 (d, 2H, $J = 8$Hz, ArH), 8.05 (d, 1H, $J = 11.4$ Hz, H-4) ppm.

$^{13}$C NMR (75.47 MHz, CDCl$_3$) = 55.55, 85.48, 111.5, 113.47, 118.05, 119.68, 121.7, 123.94, 130.13, 136.46, 151.01, 154.66, 159.93 ppm.

GCMS m/z = 246(M+2)$^+$, 244(M$^+$).

IR (KBr) $\nu_{\text{max}}$ = 2222, 1589, 1350, 768 cm$^{-1}$.

2-Chloro-5-methyl-6-phenylnicotinonitrile 117g was obtained by the reaction of propiophenone 115g (134 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow colored crystals; mp 80-82°C; yield 181 mg (79%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta = 2.59$ (s, 3H, CH$_3$), 7.30-7.34 (m, 2H, Ar), 7.36 (s, 1H, H-4), 7.44-7.51 (m, 3H, Ar).

$^{13}$C NMR (75.47 MHz, CDCl$_3$) = 17.07, 82.3, 112.4, 114, 128.68, 129.67, 130.26, 130.96, 136.24, 151.89, 157.2 ppm.
FABMS m/z (%) = [230 (M+2)+, 12], 229 [(M+1)+, 57], 228 (M+, 40), 193 (80), 192 (35), 165 (42), 154 (98), 136 (100), 121 (55), 107 (90).

IR (KBr) $\nu_{max} = 3036, 2222, 1566, 1292, 925$ cm$^{-1}$.

**2-Chloro-6-(2-thienyl)nicotinonitrile 117h** was obtained by the reaction of 1-(2-thienyl)-1-ethanone 115h (252 mg, 2 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (198 mg, 3 mmol) as yellow colored crystals; mp 140-142°C; yield 22 mg (5%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta = 7.16-7.2$ (m, 2H), 7.63 (d, 1H, $J = 5.2$ Hz), 7.7 (d, 1H, $J = 3.2$ Hz), 7.96 (d, 1H, $J = 12$ Hz) ppm.

$^{13}$C NMR (75.47 MHz, CDCl$_3$) = 83.6, 111.7, 113.5, 117.1, 129.1, 132, 132.8, 139.9, 143.2, 153.9 ppm.

GCMS m/z = 222(M+2)+, 220 (M+). IR (KBr) $\nu_{max} = 3082, 2222, 1570, 1211, 840$ cm$^{-1}$.

**2-Chloro-6-(2-naphthyl)nicotinonitrile 117i** was obtained by the reaction of 1-(2-naphthyl)-1-ethanone 115i (170 mg, 1 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow crystalline solid; mp 152-154°C; yield 246 mg (93%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta = 7.41$ (d, 1H, $J = 11.4$ Hz, H-4), 7.47-7.66 (m, 2H, ArH), 7.85-7.96 (m, 4H, ArH), 8.10 (d, 1H, $J = 11.4$ Hz, H-4), 8.35 (s, 1H, ArH) ppm.
\( ^{13}\text{C} \) NMR (75.47 MHz, CDCl\(_3\)) \( \delta = 84.86, 111.602, 113.337, 119.37, 122.99, 127.44, 127.70, 128.84, 128.90, 129.29, 129.62, 131.92, 134.85, 150.94, 154.59, 157.92 \) ppm.

EIMS m/z (%) = 266 \([\text{M}+2]^+, 14\], 264 \([\text{M}^+, 42]\), 240 \([1]\), 238 \([5]\), 230 \([34]\), 203 \([22]\), 201 \([39]\), 175 \([18]\), 150 \([13]\), 127 \([12]\), 114 \([21]\), 101 \([23]\).

IR (KBr) \( \nu_{\text{max}} = 2961, 2220, 1580, 1011, 480.6 \text{ cm}^{-1} \).

3.5.2. Reaction of \( \alpha \)-tetralone with Vilsmeier-Haack reagent in the presence of malononitrile: Synthesis of 2-chloro-5,6-dihydrobenzo[h]quinoline-3-carbonitrile 122

**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 \( \alpha \)-tetralone (1 mmol) was added and the solution was stirred at room temperature for 12 hours. To this malononitrile (1g, 1.5 mmol) was added and the reaction mixture was further heated at 90°C for 2 hours. The reaction mixture was cooled, poured over ice-cold K\(_2\)CO\(_3\) solution and extracted with diethyl ether (3 \( \times \) 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 (97:3) solvent mixture as the eluent.
2-Chloro-5,6-dihydrobenzo[h]quinoline-3-carbonitrile 122 was obtained by the reaction of 3,4-dihydro-1(2H)-naphthalenone 121 (146 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow colored crystals; mp 146-148°C; Yield 210 mg (87%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 2.96 (t, 2H, $J = 4$ Hz, CH$_2$), 3.05 (t, 2H, $J = 4$ Hz, CH$_2$), 7.24 (d, 1H, $J = 9$ Hz, Ar), 7.30-7.45 (m, 2H, Ar), 7.81 (d, 1H, $J = 9$ Hz, Ar), 8.21 (s, 1H, H-4).

$^{13}$C NMR (75.47 MHz, CDCl$_3$) = 25.2, 26.9, 82.3, 112.6, 114.4, 127.4, 127.8, 128.9, 131.3, 132, 138.3, 144.9, 155.4 ppm.

FABMS m/z (%) = 242 [(M+2)$^+$, 20], 240 (M$^+$, 95), 239 (47), 226 (20), 219 (100), 218 (92), 205 (45), 203 (24), 154 (52), 149 (85), 136 (35).

IR (KBr) $\nu_{\text{max}}$ = 2950, 2214, 1524, 1280, 964 cm$^{-1}$.

3.5.3. Reaction of benzylidene acetones with Vilsmeier-Haack reagent in the presence of malononitrile: Synthesis of 2-chloro-6-[(E)-2-phenylethenyl]pyridine-3-carbonitriles 124a-c

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 benzylidene acetone (1 mmol) was added and the solution was stirred at room temperature for 12 hours. To this malononitrile (1g, 1.5
mmol) was added and the reaction mixture was further heated at 90°C for 2 hours. The reaction mixture was cooled, poured over ice-cold K₂CO₃ 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 (97:3) solvent mixture as the eluent.

2-Chloro-6-[(E)-2-phenylethenyl]pyridine-3-carbonitrile 124a was obtained by the reaction of (E)-4-phenyl-3-buten-2-one 123a (146 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow colored crystals; mp 174-176°C; yield 58 mg (24%).

¹H NMR (300 MHz, CDCl₃) δ = 6.93 (d, 1H, J = 12 Hz, H-5), 7.04 (d, 1H, J = 15 Hz, vinylic), 7.40-7.60 (m, 6H, Ar), 8.02 (d, 1H, J = 12 Hz, H-4).

¹³C NMR (75.47 MHz, CDCl₃) = 83.9, 111.7, 113.5, 122.8, 124.8, 128.3, 129.2, 130.9, 134.6, 142.5, 148.8, 154 ppm.

FABMS m/z (%) = 242 [(M+2)+, 8], 240 (M⁺, 27), 219 (48), 205 (25), 203 (20), 165 (28), 154 (100), 136 (85), 128 (20), 115 (40), 107 (40), 105 (37).

IR (KBr) ν_max = 2220, 1562, 1199, 1146, 957 cm⁻¹.
2-chloro-6-[(E)-2-(4-chlorophenyl)ethenyl]pyridine-3-carbonitrile 124b was obtained by the reaction of (E)-4-(4-chlorophenyl)-3-buten-2-one 123b (181 mg, 1 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (99 mg, 1.5 mmol) as yellow colored crystals; mp 184-186°C; yield 160 mg (58%).

$^1$H NMR (300 MHz, CDCl$_3$); δ = 6.93 (d, 1H, J = 15 Hz, vinylic). 7.00 (d, 1H, J = 15 Hz, vinylic) 7.39-7.54 (m, 5H, Ar and H-5), 8.00 (d, 1H, J = 12 Hz, H-4).

$^{13}$C NMR (75.47 MHz, CDCl$_3$) = 84.4, 111.7, 113.4, 123.2, 125.4, 129.3, 129.5, 133.2, 136.8, 140.7, 148.3, 153.8 ppm.

FABMS m/z (%) = 276 [(M+2)$^+$, 45], 274 (M$^+$, 55), 259 (50), 239 (40), 219 (100), 217 (25), 203 (20), 178 (15), 165 (27), 154 (98), 136 (95), 120 (24), 107 (47), 89 (38).

IR (KBr) $\nu_{\text{max}} = 2222, 1558, 1204, 1087, 814$ cm$^{-1}$.

2-chloro-6-[(E)-2-(4-methoxyphenyl)ethenyl]pyridine-3-carbonitrile 124c was obtained by the reaction of (E)-4-(4-methoxyphenyl)-3-buten-2-one 123c (1.056 g, 6 mmol) with Vilsmeier-Haack reagent in the presence of malononitrile (594 mg, 9 mmol) as red colored crystals; mp 148-150°C; yield 30 mg (2%).
**1H NMR** (300 MHz, CDCl$_3$): $\delta = 3.92$ (s, 3H, OCH$_3$), 6.80-6.97 (m, 4H, Ar and vinylic), 7.40-7.55 (m, 3H, Ar and H-5), 8.00 (d, 1H, $J = 12$ Hz, H-4).

**13C NMR** (75.47 MHz, CDCl$_3$) = 55.5, 82.5, 114.7, 121.5, 122.6, 127.4, 130.2, 142.4, 149.3, 150.6, 151.4, 154.1 ppm.

**FABMS** m/z (%) = 272 [(M+2)$^+$, 15], 270 (M$^+$, 57), 259 (12), 257 (10), 154 (100), 136 (90), 120 (15), 107 (26), 89 (22), 82 (5), 80 (3).

**IR (KBr)** $\tilde{\nu}_{max}$ = 2220, 1555, 1265, 1177, 818 cm$^{-1}$.

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