CHAPTER 1

Introduction

Carbon-carbon bond formation and cyclization reactions have a major role in organic synthesis.\textsuperscript{1} A variety of carbon-carbon bond forming reactions are reported in the history of synthetic organic chemistry. Among them, Vilsmeier-Haack reaction has a special reference to its versatility and supremacy. The Vilsmeier-Haack reaction is a very useful and general method applied for the formylation of electron rich aromatic and aliphatic compounds.\textsuperscript{2} Some of the major applications of Vilsmeier-Haack reagent, chloromethyleneiminium salt in reactions such as acylation, halogenation, haloalkylation, haloformylation, dehydration, aromatization and annulations have already been reported.\textsuperscript{3} The electron deficient nature of chloromethyleneiminium salts is the key driving force for these reactions. The Vilsmeier-Haack reagent was prepared from ice cold DMF 1 and POCl\textsubscript{3} 2 by stirring at room temperature for 20 minutes and subsequent addition of the substrate to the mixture as is the case. The mechanism of the formation of Vilsmeier-Haack reagent known as the chloromethyleneiminium salt is described below (Scheme 1).

\begin{center}
\textbf{Scheme 1}
\end{center}

The reagent also finds excellent application in cycloaddition reactions. But the ability of Vilsmeier-Haack reagent to generate a broad spectrum of iminium species provides a considerable scope and versatility for the intramolecular cyclization by iminium species under Vilsmeier-Haack reaction condition. This ability of Vilsmeier-Haack reagent has been efficiently used for the synthesis of a
number of heterocycles. Recently we have shown that the Vilsmeier-Haack reaction can be effectively used for the formylation reactions of \( \alpha \)-oxoketene dithioacetals. Many more one-pot reactions were already reported under Vilsmeier-Haack reaction condition for the generation of functionalized heterocycles. Thus a detailed explanation for the dominant nature of Vilsmeier-Haack reaction in organic synthesis is beyond our limits and lot of investigations and explanations are required for each Vilsmeier-Haack mediated reaction.

### 1.1 Vilsmeier-Haack Reactions of 3-Oxo-2,3-diphenylpropanals: Synthesis of 3-Chloro-1,2-diaryl-2-propen-1-ones

Vilsmeier-Haack reagent can effectively react at electron rich centers like active methylene compounds, and usually the outcome will be formylation or a haloene bond formation. The reaction proceeds through the enolization of the methylene group followed by attack of the halide anion on the carbonyl center or the attack of Vilsmeier-Haack reagent at the methylene carbon and competition between these attacks depends on the molecular structure and electron density at the centers. There are many earlier reports indicating that Vilsmeier-Haack reagent can effectively react with enolizable ketones or active methylene compounds forming haloene derivatives in good yields. Eventhough there are many other reagents already in use for the synthesis of haloenones, it is interesting to note that synthesis of haloenones via Vilsmeier-Haack reaction was not reported till Laurent and coworkers synthesized \( \beta \)-chloroenones 5 from diketones 4 under Vilsmeier-Haack reaction condition (Scheme 2).

![Scheme 2](image-url)
Earlier in 1978, Echigo and Mukaiyama reported that reaction of enolizable aldehydes $6$ with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate $7$ in presence of triethylamine can afford vinyl chlorides $8$ in good yields (Scheme 3). In the report they have illustrated the synthesis of 3-chloro-1,2-diphenyl-2-propen-1-one. As a part of our investigations on the reactions of 3-oxo-2,3-diarylpropanals$^{10}$ and in the synthetic applications of Vilsmeier-Haack reaction$^{11}$, the outcome of the reaction of 3-oxo-2,3-diarylpropanals with Vilsmeier-Haack reagent was investigated.

With the facts discussed above in mind, 3-oxo-2,3-diphenylpropanal $9$ was treated with 1.5 equivalents of the Vilsmeier-Haack reagent at room temperature for 20 hrs (Scheme 4). The product was isolated and purified by column chromatography and characterized using IR, GCMS, $^1$H NMR and $^{13}$C NMR spectra and CHNS analysis. Based on the spectral analyses and CHNS data the product was identified as 3-chloro-1,2-diphenyl-2-propen-1-one $10$ with both E and Z forms in 1:1 isomeric ratio. The reaction was repeated with different aryl substituted 3-oxo-2,3-diarylpropanals based on the above optimized conditions. All the details including experimental as well as the characterizations were deeply explained in Chapter 3. The results obtained above reveal that the newly developed method is an efficient one for the synthesis of 3-chloro-1,2-diaryl-2-propen-1-ones, from easily available starting materials 3-oxo-2,3-diarylpropanals and Vilsmeier-Haack reagent, in excellent yields.
1.2 Reaction of 3-chloro-1,2-diaryl-2-propen-1-ones with guanidine hydrochloride: Synthesis of 4,5-diaryl-2-pyrimidinamines

Bielectrophiles are very important in the synthesis of functionalized heterocycles and carbocycles. They play a crucial role in the synthesis of a number of heterocycles. The 3-chloro-1,2-diaryl-2-propen-1-ones are a kind of 1,3-bielectrophiles. Depending on the structure of the bielectrophiles, they can be effectively used in the synthesis of five membered or six membered or seven membered heterocycles. Even though there are plenty of reactions reported about the synthetic applications of organic halides and haloenes, there is little report about the synthetic applications of β-chloroenones. There are some reports about the synthesis of heterocycles from its isomeric derivative known as chloroenals. But we cannot compare the reactivity between chloroenals and β-chloroenones, because the electron flow between the two functional groups will be different in both molecules even though they are isomers.

The synthesis of pyrimidinamine starting from deoxy benzoins has been reported. The deoxybenzoins were treated with formylating agents and the product propanals obtained on treatment with guanidine hydrochloride underwent cyclization giving 4,5-diaryl-2-pyrimidinamines (Scheme 5). But the starting material deoxybenzoin is not a readily available material. Usual methods for the synthesis of deoxybenzoins result in poor yields and require hazardous conditions. Another problem with deoxybenzoin as a starting material is that introduction of two different aroyl groups is not possible from the normal methods of synthesis. Hence it is difficult to get the products with different aroyl groups from this starting material. Further, synthesis of 4,5-diaryl-2-
pyrimidinamines from this compound encounters complications in the reaction series shown in the report. These problems can be overcome by selecting the 3-chloro-2,3 diaroylpropen-1-ones as the starting material.

![Scheme 5](image)

Studies were done to find the outcome of the reactions of the newly developed β-chloroenones, 3-chloro-1,2-diaryl-2-propen-1-ones 10 with binucleophiles. To the first leap we treated the 3-chloro-1,2-diphenyl-2-propen-1-ones with guanidine hydrochloride. A recent report from our laboratory has shown that α-formylketene dithioacetals can be effectively transformed into pyrimidine-5-carbaldehydes by treating with guanidine or benzamidine in acetonitrile at 78°C for 20 hours. So we followed the procedure by treating 3-chloro-1,2-diphenyl-2-propen-1-ones with guanidine hydrochloride 12 in acetonitrile in presence of anhydrous potassium carbonate at 78°C for 10 hours (Scheme 6). The product was isolated and characterized using IR, GCMS, 1H NMR & 13C NMR spectra and CHNS analysis and the structure of the compound was found as 4,5-diphenyl-2-pyrimidinamine 13. The reaction was repeated with various aryl substituted 3-chloro-1,2-diaryl-2-propen-1-ones and the corresponding 4,5-diaryl-2-pyrimidinamines were isolated in excellent yields. The reaction of 3-chloro-1,2-diphenyl-2-propen-1-ones was repeated with S-methylisothiourea 14 and the same procedure was repeated, and the expected product 2-(methylsulfanyl)-4,5-diphenylpyrimidine 15 was isolated.
(Scheme 7). The product was characterized using IR, GCMS, $^1$H NMR & $^{13}$C NMR spectra and CHNS analysis. All the experimental and analytical details are deeply explained in Chapter 4. This general reaction is a good example for the application of β-chloroenones in the synthesis of functionalized pyrimidines.

Scheme 6

1.3 Reactions of 3-chloro-1,2-diaryl-2-propen-1-ones with malononitrile: Synthesis of 2-hydroxy-5,6-diarylnicotinonitriles

The synthesis of 2-pyrimidinamines discussed above has shown that binucleophiles can effectively react with 3-chloro-1,2-diaryl-2-propen-1-ones and transform into functionalized heterocycles. There are many recent reports for the efficient use of ketene dithioacetals in the synthesis of functionalized pyridine derivatives.$^{17}$ A recent report from our laboratory has shown that α-formylketene dithioacetals can be efficiently transformed into functionalized nicotinonitrile in good yields by treating with malononitrile in ammonium acetate/acetic acid medium at 70°C.$^5$ Another recent report from our laboratory has shown that α-formylketene dithioacetals can be transformed into pyridone derivatives by treating with cyanoacetamide under two different reaction conditions.$^{18}$ With the above results indicated, we were in search to find an alternative for ketene dithioacetals
and α-formylketene dithioacetals. With the mentioned result, we decided to treat 3-chloro-1,2-diphenyl-2-propen-1-ones 10 with malononitrile.

As a continuation to our expedition in the synthesis of functionalized pyridine derivatives, we treated 3-chloro-1,2-diphenyl-2-propen-1-ones 10 with malononitrile in ammonium acetate/acetic acid mixture at 78 °C for 13 hrs (Scheme 8). The major product was isolated and was characterized using IR, GCMS, 1H NMR & 13C NMR spectral analyses and CHNS data as 2-hydroxy-5,6-diphenylnicotinonitrile 16. This one step synthesis of pyridone derivative was very interesting and we repeated the reaction with various 3-chloro-1,2-diaryl-2-propen-1-ones and 2-hydroxy-5,6-diarylnicotinonitriles 16 were obtained and all the data including experimental and analytical were discussed deeply in Chapter 5. The synthesis of functionalized 2-hydroxy-5,6-diarylnicotinonitriles 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.

**Scheme 8**

### 1.4 Reactions of 3-oxo-2,3-diarylprompanals with cyanoacetamide under Vilsmeier-Haack reaction condition: Synthesis of 2-chloro-5,6-diarylnicotinonitriles

Typically the reactions of active methylene compounds with Vilsmeier-Haack reagent afford β-chloromethyleneiminium salts or β-chlorovinylaldehydes, which have been recognized as useful intermediates in heterocyclic synthesis.\(^ {19}\) Recently it has been shown from our laboratory that under Vilsmeier-Haack reaction condition, ketones 17 can effectively react with nucleophiles followed by intramolecular cyclization to form functionalized nitrogen heterocycles 18.
The reaction is believed to be proceeding through functionalized chloromethyleneiminium salt intermediates followed by attack of malononitrile at the intermediates, resulting in the formation of adducts. These adducts undergo intramolecular cyclization with elimination of dimethylamine and 1,3-shift of the chlorine atom followed by aromatization affording 2-chloronicotinonitrile.

![Scheme 8](image)

Another work from our laboratory reports that 2-aryloyl-3,3-bis(alkylsulfanyl)acrylaldehydes 19 on treatment with malononitrile in presence of ammonium acetate in acetic acid undergo Knoevenagel condensation resulting in 2-[2-aryloyl-3,3-bis(methylsulfanyl)-2-propylidene]malononitriles 20, a kind of substituted butadiene which on further treatment with concentrated hydrochloric acid in refluxing methanol gave 5-aryloyl-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile 21 (Scheme 9).

![Scheme 9](image)

The 3-oxo-2,3-diphenylpropanal 9 was then treated with Vilsmeier-Haack reagent and followed the same procedure for the synthesis of 3-chloro-1,2-diphenyl-2-propen-1-one 10. After the formation of the product 10, we further treated with malononitrile or cyanoacetamide at 70°C for 3 hours in the same pot without isolating the intermediate and thus the reaction was allowed to proceed under Vilsmeier-Haack reaction condition. The product was isolated and was
characterized using IR, GCMS, $^1$H NMR and $^{13}$C NMR spectra and CHNS analysis as 2-chloro-5,6-diphenylnicotinonitriles 22 (Scheme 10). Then the reaction was repeated with various 3-oxo-2,3-diarylpropanals. The above reaction was repeated with malononitrile and it is found that treating 3-oxo-2,3-diarylpropanals 9 with either cyanoacetamide or malononitrile to give 2-chloro-5,6-diarylnicotinonitriles 22b-f. All the experimental and analytical details are described in Chapter 6. In conclusion we could synthesise functionalized nicotinonitriles in good yield by a novel method and the mechanism of the reaction is based on the general Vilsmeier-Haack reaction. This synthesis is another application of Vilsmeier-Haack reaction in the synthesis of functionalized heterocycles.

\[ \text{9} \xrightarrow{1. \text{POCl}_3 / \text{DMF, rt., 2 hr}} \text{22} \]

**Scheme 10**

### 1.5 Reactions of 3-chloro-1,2-diaryl-2-propen-1-ones with sodium azide: Synthesis of 3-oxo-2,3-diarylpropanenitriles

So far we have discussed the reactions of (E or Z)-3-chloro-1,2-diphenyl-2-propen-1-one with binucleophiles. The reactions of this compound with mono-nucleophiles such as halo, amino and azide compounds were not investigated. In our earlier literature search, we noted that 3-chloro-2-phenyl-1H-inden-1-ones 23 were effectively transformed into indolone derivatives 24 by treating with sodium azide in acetonitrile at room temperature (Scheme 11). On the basis of this report, we expected a new method for the generation of functionalized indole derivatives. Earlier reports suggest that azides can easily attack at electron deficient carbon atoms and azide itself can be considered as a nitrogen atom donor because of the easiness of releasing a nitrogen molecule from the azide attacked intermediate and possibility for further rearrangement in the molecule.

\[ \text{R}_1 \text{R}_2 \text{O} \xrightarrow{2. \text{Cyanoacetamide / Malononitrile, } 70^\circ \text{C, 3 hrs}} \text{CN} \]

\[ \text{R}_1 \text{R}_2 \text{N} \xrightarrow{3. \text{Aq. K}_2\text{CO}_3} \text{Cl} \]

\[ \text{9} \xrightarrow{1. \text{POCl}_3 / \text{DMF, rt., 2 hr}} \text{22} \]

**Scheme 10**
In the above mentioned reaction the starting material used contains 3-chloro-2-propenone moiety and hence it is decided to apply the reaction as in 3-chloro-1,2-diphenyl-2-propen-1-one 10. 3-Chloro-1,2-diphenyl-2-propen-1-one 10 was treated with sodium azide in acetonitrile at room temperature and cooled to 0°C and stirred at room temperature for 3 hours (Scheme 12). The crude product was isolated and characterized using IR, GCMS, $^1$H NMR & $^{13}$C NMR spectra and CHNS analysis as 3-oxo-2,3-diphenylpropanenitrile 25a. The reaction was repeated with various 3-chloro-1,2-diaryl-2-propen-1-ones and the products were various 3-oxo-2,3-diarylpropanenitriles. The experimental as well as the analytical details are discussed in Chapter 7. This reaction needs more studies and further works are still going in our laboratory. But this reaction can be considered as a general reaction for the synthesis of 3-oxo-2,3-diaarylpropanenitriles, because no other straight forward methods are available so far for the synthesis of the molecule. The importance of this reaction is that it offers the synthesis of good intermediates for the synthesis of functionalized heterocycles.
1.6 References


