1.1. Introduction

Though synthetic organic chemistry has developed in a fascinating way over the past decades its public image has been deteriorated due to the fear that chemistry could negatively influence the ecological balance. The synthesis of complex molecules are traditionally performed by a sequence of separate reaction steps-each step requiring its own conditions, reagents, solvents and catalysts. After each reaction step is complete the solvent and the waste products are removed and discarded, and the desired intermediate product is separated and purified. Now, environmental and economic pressures are forcing the chemical community to search for more efficient ways of performing chemical transformations. 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.\textsuperscript{1} It is obvious that these types of reactions would allow the minimization of waste; thus making the waste management more economical, as compared to stepwise reactions and the amount of solvents, reagents, adsorbents and energy would be dramatically decreased. In addition, the amount of labor involved would go down. Thus multicomponent reactions would allow an ecologically and economically favorable production.
Multicomponent reactions are among the most often applied methodologies to fulfill the modern requirements for the compound ensembles of different substitution patterns. Such reactions have been modified into a large extent for synthesizing heterocyclic compounds, amino acid derivatives, β-lactams, phosphorous triesters etc. Multicomponent reactions have also been used by Gobel and Ugi, for the generation of carbohydrate combinatorial libraries. In 1995 the libraries of U-4CR products were industrially introduced by Weber et al., and since then this chemistry is one of the most favorable strategies for searching new suitable chemical products. Many researchers are interested in developing new methods for the synthesis of heterocyclic compounds following a multicomponent strategy. A brief review of important multicomponent reactions for the synthesis of biologically active molecules have been described in Chapter 2 of the thesis. In our laboratory 2-chloronicotinonitriles were synthesized by intercepting chloromethyleneiminium salt intermediate (Vilsmeier-Haack reagent) with α-oxoketene dithioacetals and malononitrile (Scheme 1). Further investigations on this reaction showed that the new methodology could be elaborated to other enolizable ketones and chalcones leading to the synthesis of a variety of 2-chloronicotinonitriles and the results of these reactions are the subject matter of present thesis.

1.2. Vilsmeier-Haack Reaction

The reactions which involve electrophilic substitutions of electron rich aromatic substrates with N,N-dimethylchloromethyleneiminium
chloride prepared from inorganic acid halides like phosphorous oxychloride (POCl$_3$) and N,N-dialkylformamides are the classical Vilsmeier-Haack reactions. A large number of aromatic and aliphatic substrates, particularly carbonyl compounds containing methyl or methylene groups adjacent to the carbonyl group undergo iminoalkylation by the Vilsmeier-Haack reagent to afford iminoalkylated intermediates, which on aqueous work up are transformed into corresponding aldehyde derivatives. The broad synthetic utility of these iminium salts has been widely exploited for iminoalkylation followed by cyclizations, producing a variety of heterocyclic compounds. However, the present strategy for a three-component reaction involving chloromethyleneiminium salt intermediate, enolizable ketones and malononitrile gives new dimensions to Vilsmeier-Haack reaction.

1.3. Chloromethyleneiminium salt mediated three-component reactions of enolizable ketones for the synthesis of nicotinonitriles

Pyridines are an important class of compounds present in numerous natural products such as quinoline and isoquinoline alkaloids and nicotine and its analogues. Several pyridine derivatives display useful biological activities and have found applications as herbicides, fungicides, insecticides etc. Some of them are important drugs used for regulation of arterial pressure and cholesterol levels in blood. 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 and thus numerous methods have been developed for their convenient synthesis. In Chapter 3 of the thesis we have discussed a three-component reaction involving chloromethyleneiminium salt intermediate, enolizable ketones and
malononitriles leading to the synthesis of 2-chloronicotinonitriles (Scheme 2).

We have described important reactions involving chloromethyleneiminium salt or their synthetic equivalents for the synthesis of pyridines and their derivatives in this chapter.

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\begin{align*}
\text{R}^1 & = \text{alkyl}, \\
\text{R}^2 & = \text{H or CH}_3
\end{align*}
\]

Scheme 2

1.4. Lewis acid mediated Michael addition of malononitrile to chalcones: A facile method for the synthesis of 2-chloropyridines and 2-pyridones

As a part of ongoing research in our laboratory, chalcones were treated with malononitrile under Vilsmeier-Haack reaction condition. Mechanistic studies on the reaction proved that malononitrile is added to chalcones in the presence of Vilsmeier-Haack reagent to yield bis(aryl)-2-chloronicotinonitriles and in the presence of POCl\textsubscript{3} to yield 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 get chlorovinyl amines. These results are described in Chapter 4 of the thesis (Scheme 3).
1.5. An unprecedented method for the synthesis of 2-pyridones from 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes

An important analogue of milrinone, 5-aroyl-2-oxo-3-pyridinecarbonitrile was synthesized in our laboratory from aroylformyl ketenedithioacetal 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. Although literature review showed that 2-pyridones could be synthesized via Knoevenagel reaction followed by in situ cyclization of the adduct under basic or acidic conditions, the adducts 2-[2-aroyl-3,3-bis(methylsulfanyl)-2-propyldene]malononitriles were reluctant to cyclization under most of the reaction conditions. Detailed investigations on the above reaction caused to develop a one-pot method for the synthesis of 2-pyridones and it is the subject matter of Chapter 5 of the thesis (Scheme 4).
Usually 2-pyridone derivatives exist in a pyridone-pyridol equilibrium and most of their crystalline properties and thus electronic properties are explained by three-dimensional array of 2-pyridone molecules. Structure determination and refinement of 2-hydroxy-5-(4-methoxybenzoyl)-6-(methylsulfanyl)nicotinonitrile has also been given in Chapter 5 of the thesis.

1.6. Conclusion

The present thesis describes interesting reactions involving functionalized chloromethyleneiminium salt intermediates for the synthesis of pyridine derivatives. The interception of malononitrile with functionalized chloromethyleneiminium salt formed from enolizable ketones and chalcones led to the formation of functionalized 2-chloronicotinonitriles. Mechanistic investigations on the reaction of chalcones with malononitrile under Vilsmeier-Haack condition led to the development of new methods for the synthesis of 2-hydroxy-4,6-bis(phenyl)nicotinonitriles and chlorovinyl amines from chalcones. Besides, 5-aryloxy-2-hydroxy-6-(methylsulfanyl) nicotinonitriles were prepared from arylformyl ketene dithioacetals and malononitrile by a one-pot method. In conclusion these reactions have explored new possibilities of Vilsmeier-Haack reagent in three component reactions.

1.7. References


