Chapter 6

Chloromethyleneiminium salt mediated three component reactions: Synthesis of substituted 2-chloronicotinonitriles

6.1 Introduction

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 is complete the solvent and the waste products are removed and discarded, and the 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 required structures. 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 the amount of solvents; reagents, adsorbents and energy would be dramatically decreased. In addition the amount of labor involved would go down. Thus these reactions would allow an ecologically and economically favorable production. We have developed a chloromethyleneiminium salt mediated, three-component methodology, leading to the formation of substituted 2-chloronicotinonitriles from α-oxoketene dithioacetals and β-enaminoketones and these results are described in this chapter.
6.1.1 Multicomponent reactions

Multicomponent reactions are among the most often applied methodologies to fulfill the modern requirements for the compound ensembles of different substitution patterns. The library chemistry became active in 1982 when Furka introduced the peptide libraries, which are formed by the multistep solid phase method of Merrifield, and in the following years other solid phase libraries were also introduced.\(^2\) In solution phase, Ugi et al. introduced a new route to synthesize amino acid libraries by a four-component reaction which is known as U-4CR.\(^3\) A U-4CR usually involves a combination of a carboxylic acid, an amine, an aldehyde and an isocyanide to afford highly substituted amino acids 5 (Scheme 1).

\[
\begin{align*}
R^1\text{COOH} + R^2\text{NH}_2 + R^3\text{R}^4 + R^5\text{NC} & \rightarrow R^1\text{N}^2\text{R}^3\text{R}^4\text{O}^5\text{R}^6
\end{align*}
\]

Scheme 1

Many types of the U-4CR and its combinations with further reactions have been developed. Such reactions have been modified into a large extent for synthesizing important amino acid derivatives, β-lactams\(^4\) or phosphorous triesters.\(^5\) Multicomponent reactions have also been used by Gobel and Ugi, for the generation of carbohydrate combinatorial libraries.\(^6\) In 1995 the libraries of U-4CR products were industrially introduced by Weber et al.,\(^7\) and since then this chemistry is one of the most favorable strategies for searching new suitable chemical products.\(^8\)

It is not only the primary U-4CR products that can form extensive libraries but the substances obtained in various subsequent reactions are also of great interest. For example, Keating et al. have reported a synthesis of substituted pyrroles 9 starting from the cyclohexenamide 6. The acid catalyzed cyclization of 6 gave the 1,3-dipole 7 which on cycloaddition with acetylenic dienophiles gave the adduct 8 which on loss of carbon dioxide afforded pyrroles 9 (Scheme 2).\(^9\)
Reaction of methyl trimethylsilyloxy cyclopropane carboxylates 10 with amino acids 11, tert-butylisonitrile and methanol furnished amino diacid derivatives 12 as the result of an Ugi-5-center-4-component reaction. The adduct 12 could be thermally cyclized to provide γ-lactams 13 in good yields (Scheme 3).  

Isomers of the antibiotic furanomycin 18 and 19 have been prepared in 55% overall yield via a Ugi four component condensation reaction of the trans-aldehyde 14 (Scheme 4).
Balme et al. have reported a three component synthesis of stereo defined 4-benzylidene-(or alkenylidene)-pyrrolidenes 23 from simple, readily available starting materials. This one pot process is initiated by a conjugate addition of a propargylamine to a gem-diactivated olefin subsequently followed by a carbopalladation involving an aryl halide (or vinyl triflate) (Scheme 5).12

This new reaction conditions have been applied to a series of propargyl amines, aryl halides and gem-diactivated olefins in order to probe the scope and limitations of three component reactions. They have synthesized a symmetrical product 27 using 1,4-diiodobenzene 26 as a bis-coupling species in the above reaction (Scheme 6).13

Recently biologically active α-oximinoamides 31 have been prepared by a simple three-component reaction between nitro derivatives, isocyanides and acetic anhydride (Scheme 7).13
The reaction of an aldehyde, malononitrile and phenol in water at reflux in the presence of cetyltrimethylammonium chloride (CTACl) as catalyst affords a one pot synthesis of 2-amino-2-chromenes 35 (Scheme 8).\(^{14}\)

\[
R'CHO + \text{CN} + \text{OH} \xrightarrow{\text{CTACl, H}_2\text{O}} R^1CN\text{NH}_2
\]

**Scheme 8**

Similarly one pot condensation of α,β-unsaturated ester 36, amidine and malononitrile/cyanoacetate building blocks affords multifunctionalized pyrido[2,3-d]pyrimidine scaffolds 39 (Scheme 9).\(^{15}\)

\[
\text{MeO}_2\text{C} + \text{CN} + \text{NH}_2 + \text{NH}_2R^4 \xrightarrow{\text{NaOMe, MeOH, Microwave conditions}} \text{R}^1\text{N}R^2R^3R^4
\]

**Scheme 9**

The reaction of N-silylated iminoethers with 2-substituted acetyl chlorides yields activated 2-azadienes. They were shown to react with electron deficient acetylenic dienophiles to yield pyridones 43. The reaction of 2-azadienes with activated nitriles provided a very practical route towards polysubstituted pyrimidones 45 (Scheme 10 and 11).\(^{16}\)
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. The reaction combines aldehydes and β-ketoesters with urea to produce dihydro pyrimidinones 49 having an ester moiety in the 5-position of the heterocycle (Scheme 12).\(^\text{17}\)

A variety of 1,2,3,4-tetrahydroquinolines 53 can be prepared by a new three component condensation of an imine, an α-branched and enolizable aldehyde and a nucleophile, under ytterbium(III)trifluoromethane sulfonate [Yb(OTf)\(_3\)] catalysis (Scheme 13).\(^\text{18}\)

Nair et al. have reported MCRs involving diisopropylaminoisocyanide and DMAD.\(^\text{19}\) For example a variety of aldehydes and dicarbonyl compounds were reacted with diisopropylaminoisocyanide and DMAD leading to the formation of 1-aminopyrrolin-2-one derivatives 57 (Scheme 14).\(^\text{19a}\)
Veenstra and Schmid described a one pot, three-component condensation of an aldehyde and a carbamate with allyltrimethylsilane, to give the protected homoallyl amines 61 in high yields under boron trifluoride etherate catalysis (Scheme 14).  

Ring opening of 1-alkyl-2-methylene aziridines is accomplished with organocopper reagents in the presence of boron trifluoride diethyl etherate giving 1-substituted propan-2-ones 63 in 42-88% yield. This MCR has been applied to the synthesis of (Z)-6-heneicosan-11-one 64, an important sex attractant of the Tussock moth (Scheme 16 and 17).
The above-mentioned reactions show the diversity of multicomponent reactions for preparing synthetically important molecules in a one-pot reaction. In the present chapter we describe a one-pot three-component strategy for the formation of functionalized nicotinonitriles from $\alpha$-oxoketene dithioacetals or $\beta$-enaminoketones.

6.2 Results and discussion

The pyridine moiety is one of the important heteroaromatic ring systems present in numerous natural products and biologically active substances. The modification of the pyridine nucleus to various annulated heterocycles or naturally occurring alkaloids attracts considerable interest in organic chemistry. Halogenated pyridines are useful intermediates in drug research as they can be further elaborated to desired structure by Stille and Suzuki cross coupling reactions. Our literature survey revealed that there are only limited reports on the synthesis of 2-halopyridines, in some cases the existing heterocycles are functionalized by various halogenating reagents. Often cyclization reaction of substituted propylidene malononitriles, under acid catalyzed condition lead to the formation of 2-pyridone derivatives. In the preceding chapter we have made attempts to synthesize various functionalized nicotinonitriles from 2-aroyl-3,3-bis(methylsulfanyl)acrylaldehydes via a pushpull butadiene intermediate. Cyclization reaction of these pushpull butadienes under acidic conditions afforded pharmaceutically important 2-pyridone derivatives. In the literature there are some reports on alkylidene malononitriles, which undergo cyclization reactions under the Vilsmeier-Haack reaction conditions to afford functionalized 2-chloro pyridines. We envisioned that if a mixture of $\alpha$-oxoketene dithioacetals and malononitrile is treated with the Vilsmeier-Haack reagent, the intermediate chloromethyleneiminium salt should undergo condensation with malononitrile to afford intermediate adducts, which could be cyclized insitu to form chloro substituted nicotinonitriles.
6.2.1 Three component reaction of α-oxoketene dithioacetals with malononitrile and Vilsmeier reagent: Synthesis of 5-aryI-2-chloro-6-methylsulfanyl)nicotinonitriles (67)

The Vilsmeier-Haack reagent was prepared by the slow addition of POCl₃ (1.92 mL, 20 mmol) to DMF (16 mL, 200 mmol) at 0 °C, followed by stirring at room temperature for 15 min. A mixture of malononitrile (450 mg, 6.75 mmol) and benzoyl ketene dithioacetal 65a (1g, 4.5 mmol) was added to this reagent and stirred at room temperature for 12 h, followed by heating at 90 °C for 1h. Usual work up using aqueous saturated potassium carbonate solution, and purification by chromatography gave 5-benzoyl-2-chloro-6-(methylsulfanyl)nicotinonitrile 67a in 47% yield as a yellow crystalline solid having melting point 158-160 °C along with the adduct 66 in 15% yield (Scheme 18).

![Reaction Scheme 18](image)

<table>
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<tr>
<th>66, 67</th>
<th>Ar</th>
<th>Yield</th>
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<tr>
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<td>66</td>
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<tr>
<td>a</td>
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<tr>
<td>b</td>
<td>4-CH₃OC₆H₄</td>
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</tr>
<tr>
<td>c</td>
<td>4-ClC₆H₄</td>
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</tr>
<tr>
<td>d</td>
<td>4-NO₂C₆H₄</td>
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Scheme 18

The structure of the compound 67a was determined with the help of ¹H NMR, ¹³C NMR, GCMS and IR spectral analysis. The ¹H NMR spectrum (Fig. 1) of the compound showed resonance as a singlet at δ 7.87 H-4 proton of the
pyridine ring, triplets at δ 7.68, 7.54 and a doublet at δ 7.74 ppm for aromatic protons and a singlet of three protons at δ 2.47 for the methylsulfanyl group. The $^{13}$C NMR spectrum (Fig. 2) showed peaks at 167.49 (CO), 153.24, 142.24, 135.88, 133.98, 129.69, 129.19, 128.93, 114.54 (CN), 103.59 and 14.38 (SCH$_3$). The IR spectrum (Fig. 3) showed characteristic aromatic stretching at 2929 cm$^{-1}$ and CN absorption at 2234 cm$^{-1}$. The peaks at 1646 cm$^{-1}$ for carbonyl group and other peaks were at 1578, 1492, 1374, 1209, 1231 and 1004 cm$^{-1}$. In the EIMS spectrum (Fig. 4) the compound showed molecular ion peak at m/z 288 and M$^+$+2 peak at 290 in the ratio 3:1. The structure was confirmed by the CHN analysis (Calcd for C$_{12}$H$_8$ClN$_2$OS: C, 58.23; H, 3.14; N, 9.70; Found: C, 58.36; H, 4.51; N, 9.35).

![Figure 1](image-url)  
**Figure 1** $^1$H NMR spectrum of 5-benzoyl-2-chloro-6-(methylsulfanyl) nicotinonitrile 67a
Figure 2  $^{13}$C NMR spectrum of 5-benzoyl-2-chloro-6-methylsulfanyl nicotinonitrile 67a

Figure 3 IR spectrum of 5-benzoyl-2-chloro-6-methylsulfanyl nicotinonitrile 67a
Other substituted aroylketene dithioacetals 65b-d also gave 5-aroyl-2-chloro-6-(methylsulfanyl)nicotinonitriles 67b-d along with 2[2-aroyl-3,3-bis(methylsulfanyl)-2-propylidene]malononitrile 66b-d (Scheme 18). While p-nitrobenzoylketene dithioacetal gave the substituted nicotinonitrile 67d exclusively, the p-methoxy and p-chlorobenzoylketene dithioacetals gave adducts 66b & 66c as the major products.

The formation of 2-chloronicotinonitrile 67 and adducts 66 can be rationalized as follows. Addition of malononitrile to the intermediate iminium salt 68 formed by the iminoalkylation of the ketene dithioacetal would afford 69 which on cycloaddition induced by chloride ion would afford the nicotinonitrile 67, while loss of Me₂NH would give the adduct 66.²⁷ Alternatively the intermediate 69 can also be formed by the conjugate addition of the ketene dithioacetal to the enaminonitrile 70 that could have formed from malononitrile²⁸ in the presence of Vilsmeier-Haack reagent (Scheme 19).
The cyclic ketene dithioacetal 71 was also treated with the mixture of Vilsmeier-Haack reagent and malononitrile under similar conditions. In this case the reaction afforded only the condensation adduct, 2-[2-(1,3-dithiolan-2-yldien)3-oxo-3-phenylpropyldienemalononitrile 73 along with 2-(1,3-dithiolan-2-yldien)-1-(4-methylphenyl)-3-butene-1-one 72 (Scheme 20).
6.2.2 Reactions of β-enaminoketones with Vilsmeier-Haack reagent in the presence of malononitrile: Synthesis of 6-aryl-2-chloronicotinonitriles (81)

Treatment of β-enaminoketones 77 with Vilsmeier reagent leads to the formation of chlorosubstituted vinamidinium salt 75. Gupton et al. have exploited the reactivity of these iminium salts 75 with aminoacetates in their protocol for substituted pyroles.29 Treatment of enaminonitriles with the chlorovinamidinium salt led to the formation of substituted pyridines.30 Condensation of cyanoacetamide and the iminium salt 75 gave the substituted 2,4-pentadienoates 78 which cyclized in the presence of hydrochloric acid in acetic acid to afford 6-aryl-2-chloropyridines 79.25a We envisioned that insitu addition of malononitrile to the chlorosubstituted vinamidinium salt 75 generated from enaminoketones by Vilsmeier-Haack reactions would lead to cyclization under the reaction conditions to afford substituted nicotinonitriles 81. The Vilsmeier-Haack reagent was prepared by the slow addition of POCl₃ (1.15 mL, 12 mmol) to DMF (10 mL, 120 mmol) at 0 °C followed by stirring at room temperature for 15 min. A mixture of malononitrile (250 mg, 3.75 mmol) and 3-(dimethylamino)-1-phenyl-2-propene-1-one 77a (440 mg, 2.5 mmol) was added to this reagent and stirred at room temperature for 12 h. followed by heating at 90 °C for 1 h. Usual work up using aqueous saturated potassium carbonate solution, and purification of the crude
product by recrystallization from hexane: ethyl acetate (9:1) gave yellow colored crystals (mp 98-100 °C) of 2-chloro-6-phenyl nicotinonitrile 81a in 84% yield (Scheme 22).

![Scheme 22](image)

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<th>Yield</th>
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<tr>
<td>a</td>
<td>C₆H₅</td>
<td>84</td>
</tr>
<tr>
<td>b</td>
<td>4-CH₃OC₆H₄</td>
<td>87</td>
</tr>
<tr>
<td>d</td>
<td>2-Naphthyl</td>
<td>93</td>
</tr>
</tbody>
</table>

The ¹H NMR spectrum (Fig. 5) of 2-chloro-6-phenyl nicotinonitrile 81a showed two doublets with coupling constant 11.4 Hz, one at δ 7.29 and the other at δ 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 δ 7.79 and a multiplet of three protons at δ 7.46-7.54 for aromatic protons. The ¹³C NMR spectrum (Fig. 6) showed resonances at δ 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 EIMS spectrum (Fig. 7) of the compound showed molecular ion peak at m/z 214 and 216 (3:1) for M⁺ and M⁺+2 peaks respectively. The IR spectrum (Fig. 8) 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.
Figure 5 $^1$H NMR Spectrum of 2-chloro-6-phenylnicotonitrile 81a

Figure 6 $^{13}$C NMR Spectrum of 2-chloro-6-phenylnicotonitrile 81a
Figure 7 EIMS Spectrum of 2-chloro-6-phenylnicotinonitrile 81a

Figure 8 IR Spectrum of 2-chloro-6-phenylnicotinonitrile 81a

Other substituted enaminoketones 77b and 77c also gave corresponding 6-aryl-2-chloronicotinonitriles 81b and 81c in good yields and they were characterized on the basis of IR, $^1$H NMR, $^{13}$C NMR and EIMS spectral data.

Apparently the formation of 6-aryl-2-chloronicotinonitriles 81 can be depicted by the addition of malononitrile to the vinamidinium salt 75 to form an
adduct 80 which on chlorine induced cyclization followed by aromatization would afford 81 (Scheme 23).

\[
\text{Scheme 23}
\]

6.3 Conclusion

We have developed a facile chloromethyleneiminium salt mediated three-component domino reaction for the synthesis of 5-aryl-2-chloronicotinonitriles and 6-aryl-2-chloronicotinonitriles from \(\alpha\)-oxoketene dithioacetals and \(\beta\)-enaminoketones respectively. The new methodology is efficient to afford the expected products in good yields and this strategy can be extended to related reactions leading to the synthesis of a variety of pyridine derivatives.

6.4 Experimental

The general experimental details have been given in the experimental section of Chapter 3. \(\beta\)-Enaminoketones, were prepared according to the reported methods by heating a mixture of \(N,N\)-dimethyl formamide dimethyl acetal with corresponding ketones in a sealed tube at 120 °C for an hour.

6.4.1 Three component reaction of \(\alpha\)-oxoketene dithioacetals with malononitrile and Vilsmeier reagent: Synthesis of 5-aryl-2-chloro-6-(methylsulfanyl)nicotinonitriles (67)

General Procedure

The Vilsmeier-Haack reagent was prepared by mixing DMF (15 mL, 200 mmol) and \(\text{POCl}_3\) (1.92 mL, 20 mmol) at 0 °C followed by stirring at room temperature for 15 min. To the Vilsmeier-Haack reagent a mixture of aroylketene...
dithioacetal 65 (4.5 mmol) and malononitrile (450 mg, 6.75 mmol) was added at room temperature and stirred well for 12 hrs. Then the reaction mixture was heated to 100 °C for an hour. It was cooled, poured over ice-cold K₂CO₃ solution and extracted with diethyl ether (3 X 20 mL). The organic layer was washed with water, dried with sodium sulphate and the solvent was removed by evaporation. The crude reaction mixture was purified by column chromatography using hexane: ethyl acetate (97:3) solvent mixture as the eluent.

2-[2-Benzoyl-3,3-bis(methylsulfanyl)-2-propylidene] malononitrile 66a was obtained by the reaction of 3,3-bis(methylsulfanyl)-1-phenyl-2-propene-1-one 65a (1 g, 4.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (450 mg, 6.75 mmol) as deep yellow colored crystals; mp 114-116 °C; yield 200 mg (15%). The spectral data is given in Chapter 4.

5-Benzoyl-2-chloro-6-(methylsulphenyl)nicotinonitrile 67a was obtained by the reaction of 3,3-bis(methylsulfanyl)-1-phenyl-2-propene-1-one 65a (1 g, 4.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (450 mg, 6.75 mmol) as yellow crystalline solid; mp 158-160 °C; yield 610 mg (47%); ¹H NMR (300 MHz, CDCl₃) δ = 2.47 (s, 3H, SCH₃), 7.54 (t, 2H, J = 8Hz, ArH), 7.64 (t, 1H, J = 8Hz, ArH), 7.68 (t, 2H, J = 8Hz, ArH), 7.87 (s, 1H, H-4) ppm; ¹³C NMR (75.47 MHz, CDCl₃) δ = 14.38 (SCH₃), 103.59, 114.54 (CN), 128.93, 129.19, 129.69, 133.98, 135.88, 142.24, 153.24, 167.49 (CO ppm; EIMS m/z (%) = 290 (M⁺, 2), 288 (M⁺, 21), 273 (23), 257 (11), 255 (35), 245 (9), 197 (15), 152 (8), 105 (48), 77 (100); IR (KBr) νmax = 2929, 2234, 1646, 1578, 1492, 1374, 1209, 1231, 1004 cm⁻¹; Caled for C₁₄H₆ClN₂OS: C, 58.23; H, 3.14; N, 9.70; Found: C, 58.36; H, 4.51; N, 9.35
2-{3,3-Bis(methylsulfanyl)-4-(4-methoxybenzoyl)-2-propylidene} malononitrile 66b was obtained by the reaction of 3,3-bis(methylsulfanyl)-1-(4-methoxyphenyl)-2-propene-1-one 65b (1.15 g, 4.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (450 mg, 6.75 mmol) as deep yellow colored crystals; mp 116-118 °C; yield, 770 mg (52%). The spectral data is given in Chapter 4.

2-Chloro-5-(4-methoxybenzoyl)-6-(methylsulfanyl)nicotino nitrile 67b was obtained by the reaction of 3,3-bis(methylsulfanyl)-1-(4-methoxyphenyl)-2-propene-1-one 65b (1.15 g, 4.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (450 mg, 6.75 mmol) as yellow crystalline solid; mp 152-154 °C; yield 380 mg (27%); 1H NMR (300 MHz, CDCl3) δ = 2.58 (s, 3H, SCH3), 3.90 (s, 3H, OCH3), 6.97 (d, 2H, J = 8Hz, ArH), 7.71 (d, 2H, J = 8Hz, ArH), 7.78 (s, 1H, H-4) ppm; EIMS m/z (%) = 318 (M+, 5), 305 (2), 303 (6), 287 (4), 285 (5), 199 (5), 165 (5), 135 (18), 121 (19), 107 (13), 97 (17), 81 (29), 69 (100); IR (KBr) νmax = 2926, 2232, 1601, 1573, 1379, 1275, 1120, 1011 cm⁻¹.

2-{3,3-Bis(methylsulfanyl)-4-(4-chlorobenzoyl)-2-propylidene} malononitrile 66c was obtained by the reaction of 3,3-bis(methylsulfanyl)-1-(4-chlorophenyl)-2-propene-1-one 65c (1.2 g, 4.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (450 mg, 6.75 mmol) as deep yellow colored crystals; mp 132-134 °C; yield 315 mg (21%); The spectral data is given in Chapter 4.

2-Chloro-5-(4-chlorobenzoyl)-6-(methylsulfanyl)nicotino nitrile 67c was obtained by the reaction of 3,3-bis(methylsulfanyl)-1-(4-chlorophenyl)-2-propene-1-one 65c (1.2 g, 4.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (450 mg, 6.75 mmol) as yellow crystalline solid; mp 168-170 °C; yield 660 mg (45%); 1H NMR (300 MHz, CDCl3) δ = 2.59 (s, 3H, SCH3),
7.48 (d, 2H, J = 8Hz, ArH), 7.65 (d, 2H, J = 8Hz, ArH), 7.81 (s, 1H, H-4) ppm; EIMS m/z (%) = 326 (M+4, 5), 324 (M+2, 16), 322 (M', 23), 309 (12), 307 (21), 291 (52), 289 (73), 197 (42), 141 (20), 139 (63), 113 (31), 111 (100), 85 (21). 75 (84); IR (KBr) ν_{max} in cm⁻¹ = 3049, 2220, 1653, 1576, 1489, 1382, 1286, 1234, 1010.

2-Chloro-3-(4-nitrobenzoyl)-6-(methylsulfonyl)nicotino nitrile 67d was obtained by the reaction of 3,3-bis(methylsulfonyl)-1-(4-nitrophenyl)-2-propene-1-one 65d (1.2 g, 4.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (450 mg, 6.75 mmol) as yellow crystalline solid; mp 200-202 °C; yield 1.1 g (76%); ¹H NMR (300 MHz, CDCl₃) δ = 2.6 (s, 3H, SCH₃), 7.86 (m, 3H, ArH and H-4), 8.36 (d, 2H, J = 8Hz, ArH); EIMS m/z (%) = 333 (M', 14), 302 (12), 288 (16), 256 (14), 214 (15), 183 (35), 159 (10), 129 (18), 120 (29), 97 (83), 71 (87), 57 (100); IR (KBr) ν_{max} in cm⁻¹ = 2930, 2221, 1653, 1576, 1489, 1382, 1286, 1234, 1011.

2-(1,3-Dithiolan-2-yliden)-1-phenyl-3-buten-one 72 was obtained by the reaction of 2-(1,3-dithiolan-2-yliden)-1-phenyl-1-ethanone 71 (1g, 4.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (450 mg, 6.75 mmol) as cream coloured crystalline solid; mp 103-105 °C (reported mp 100-102 °C); yield 230 mg (20%).

2-[2-(1,3-Dithiolan-2-yliden)-3-oxo-3-phenylpropylidene] malononitrile 73 was obtained by the reaction of 2-(1,3-dithiolan-2-yliden)-1-phenyl-1-ethanone 71 (1g, 4.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (450 mg, 6.75 mmol) as deep yellow colored crystals; mp 122-124 °C; yield 860 mg (63%).

6.4.2 Reactions of β-enaminoketones with Vilsmeier-Haack reagent in the presence of malononitrile: Synthesis of 6-aryl-2-chloronicotinonitriles (81).

General Procedure

The Vilsmeier-Haack reagent was prepared by mixing DMF (10 mL, 120 mmol) and POCl₃ (1.15 mL, 12 mmol) at 0 °C followed by stirring at room
temperature for 15 min. To the Vilsmeier-Haack reagent a mixture of β-enaminoketones (2.5 mmol) and malononitrile (250 mg, 3.75 mmol) was added at room temperature and stirred for 12 hrs. Then the reaction mixture was heated at 90 °C for an hour. It 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 sodium sulphate and the solvent was removed by evaporation. The crude reaction mixture was purified by column chromatography using hexane: ethyl acetate (97:3) solvent mixture as the eluent or recrystallized from hexane-ethyl acetate.

2-Chloro-6-phenylnicotinonitrile 78a was obtained by the reaction of 3-(dimethylamino)-1-phenyl-2-propene-1-one 76a (440 mg, 2.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (250 mg, 3.75 mmol) as yellow crystalline solid; mp 98-100 °C; yield 510 mg (84%); ¹H NMR (300 MHz, CDCl₃) δ = 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; ¹³C NMR (75.47 MHz, CDCl₃) δ = 127.7, 129.0, 129.3, 131.8, 132.4, 134.9, 151.0, 154.6, 154.9 ppm; EIMS m/z (%) = 216 (11), 214 (27), 180 (18), 179 (100), 153 (12), 152 (59), 127 (5), 125 (23), 105 (4), 99 (11), 77 (22); IR (KBr) ν_max = 3040, 2220, 1580, 1447, 1342, 1196 cm⁻¹;

2-Chloro-6-(4-methoxyphenyl)nicotinonitrile 78b was obtained by the reaction of 3-(dimethylamino)-1-(4-methoxyphenyl)-2-propene-1-one 76b (520 mg, 2.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (250 mg, 3.75 mmol) as yellow crystalline solid; mp 160-162 °C; yield 590 mg (87%); ¹H NMR (300 MHz, CDCl₃) δ = 3.9 (s, 3H, OCH₃), 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,
2-Chloro-6-(2-naphthyl)nicotinonitrile 78c was obtained by the reaction of 3-(dimethylamino)-1-(2-naphthyl)-2-propene-1-one 76c (560 mg, 2.5 mmol) with the Vilsmeier-Haack reagent in the presence of malononitrile (250 mg, 3.75 mmol) as yellow crystalline solid; mp 152-154 °C; yield 680 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; \(^1^C\) 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, 132.59, 134.85, 150.94, 154.59, 157.92 ppm; EIMS m/z (%): 266 (14), 264 (42), 240 (1), 238 (5), 230 (34), 203 (22), 201 (39), 175 (18), 150 (13), 127 (12), 114 (21), 101 (23); IR (KBr) \(v_{max} = 2961, 2220, 1625, 1580, 1011, 480.6\) cm\(^{-1}\)

### 6.5 References


