CHAPTER 3
Selective Synthesis of Chloromethylpyridines and Chloropyridines

3.0 INTRODUCTION:

Pyridine is a benzene ring with one of the carbons replaced by nitrogen; There are several substituted pyridines like chloropydine and 2-chloromethylpyridine are used in pharmaceutical and also in pesticide industry. There is an immense need to make them, Which were accruing from the rapidly developing agricultural industry as a result of improved crop varieties, artificial fertilizers, and mechanization from the effects of pests and pathogens. User acceptance of crop protective agents was extraordinarily high, which is attributable to the improved quality of life they brought to the forming community as well as to the reduced economic risks.

The use of crop-protecting agents was an investments which yielded considerable returns. Chemistry in harmony with agriculture, an ordered world, an ideal partnership, or so, it appeared for a long time. However, where there is light, there must inevitably also be shadows.

3.0.1 INTRODUCTION TO (Diphasgene & Triphosgene)

Trichloromethyl chloroformate (TCF, diphosgene, 1) and bis-(trichloromethyl) carbonate (BTC, triphosgene,2) two important substitutes for phosgene, have emerged as versatile reagents for the synthesis of important classes of organic compounds. Recently, for example, large number of compounds with high biological activities have been synthesized by use of TCF and BTC.
It is well known that phosgene has long been of tremendous importance in organic chemistry for a wide variety of synthetic applications. However, it has several disadvantages: First, being a gas makes it difficult to measure accurately the amount used and to avoid side reactions when an excess is used. Second, it is a highly toxic gas, which makes its use and transportation severely restricted. Now its use has been banned in both research labs and industrial plants. In contrast, TCF is a colorless liquid and BTC is a crystalline solid. Both are soluble in common organic solvents such as ether and chloroform. TCF may be prepared by illumination of methylformate and chlorine with a 500-Watt lamp, BTC can be obtained by Councler's route or Eckert's method or by UV irradiation of dimethylcarbonate and chlorine.

Bis-(Trichloromethyl)Carbonate. Chlorine gas was bubbled into a stirred solution of dimethyl carbonate (45.0g, 0.3mol) in 250mL of carbon tetrachloride, cooled to 10-20 °C and irradiated with two lamps (philips MLU 300W) for 28 hrs of net reaction (it is possible to interrupt the reaction). The reaction was monitored by 1HNMR. Removal of the solvent in vacuum (200Torr) gave a crystalline solid which, after drying in vacuum at 0.1 Torr, afforded 143.0g (97%) of a white solid, m.p.79 °C. The HCl gas evolved was trapped into 1.6 of a 20% aqueous sodium carbonate solution.

TCF may be synthesized from methylformate or by methylchloroformate a similar procedure (Scheme.1)
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TCF may be synthesized from methylformate or by methylchloroformate a similar procedure (Scheme.1)
TCF and BTC are valuable, cost-effective substitutes for phosgene. The main reason is that they can be handled more safely and more easily than phosgene. Pasquato proposed a mechanism, shown in (Scheme 2) for the mode of action of TCF and BTC.

It was found that one equivalent of TCF can produce in situ two equivalents of phosgene, while BTC can lead to three equivalents of in situ phosgene thus making TCF and BTC safe synthetic equivalents of phosgene.

Pulay has pointed out that BTC may be converted to phosgene via a six-membered ring intermediate (Scheme 3)
Scheme 3

\[
\text{Cl-O-Cl} \xrightarrow{\text{Cl-O-Cl}} \text{Cl-O-Cl} + \text{CCl}_4 + \text{CO}_2
\]

Comparison of the reactivity of phosgene and its substitutes. It has been reported that the reactivity of phosgene is 18.7 times greater than that of TCF and 170 times that of BTC. Therefore, the reactions of both substitutes may be controlled more easily than those of phosgene.

3.1 Key applications:

Most of the chloromethylpyridines and chloropyridines constitute an important class of compounds in the preparation of pharmaceuticals, dyes, and pesticides. Most of the chloropyridines act as intermediates in pesticide industries. Haloxyfop (3) is a herbicide which is inhibitor of acetyl-CoA carboxylase. Imdacloprid (4) is an insecticide it acts against the nicotinergic acetyl choline receptor (n-ACHR). Chlorfluazuron (5) is an insecticide, it acts against the insect growth regulator and inhibitor of chitin biosynthesis. Tordon (6) used on turf to control a wide variety of grass weeds.

Fig. 2
Chapter III  Chloromethylpyridines and Chloropyridines...

3.2 General synthesis:

The two most commonly used methods for the synthesis of 2-chloromethylpyridine and chloropyridines involve direct chlorination of pyridine and pyridine N-oxide using various reagents like acetyl hypochlorite,\textsuperscript{12} POCl\textsubscript{3},\textsuperscript{13} SO\textsubscript{2}Cl\textsubscript{2},\textsuperscript{14} phosgene in DMF\textsuperscript{15} and trichloroacetyl chloride,\textsuperscript{16} etc. All these reagents generate inorganic salts and possess environmental as well as disposable problems. The proceeding of the reaction is shown in (scheme 4)

Scheme 4

According to Mary Lynne Ash \textit{et al.},\textsuperscript{17} 2-chloromethylpyridine has been prepared by the direct chlorination of 2-picoline-N-oxide treated with POCl\textsubscript{3} in presence of a base TEA shown (Scheme 5)

66
In another report Gunter E.Jeromin et al.\textsuperscript{18} reported that the chlorination of 2-methyl pyridine react with trichloroisocynuric acid (TCC) with out adding any initiator to provide the corresponding chloromethyl derivatives as shown (Scheme 6).

Barnes \textit{et al.},\textsuperscript{19} reported side chain chlorination was done in four steps for example 6-chloro-2-chloromethylpyridine synthesis is shown (Scheme 7).
3.3 Present work:

During the course of time developed a new method for side chain chlorination for picoline-N-oxide and ring chlorination for pyridine-N-oxides, using diphosgene and triphosgene are safe and stable for toxic phosgene gas. Diphosgene used in various chemical transformations such as oximes to nitriles, preparation of esters etc. Triphosgene also used in many organic reactions such as chloroformylation, carbonylation, dehydration and in the synthesis of imidazolidine-2-ones. Our continuing interest in the synthesis of pesticides and pyridinecarboxaldehydes using diphosgene and triphosgene. This was the mild and selective method for the preparation of chloromethyl pyridines (13, 14) and chloropyridines (18-21) from picoline-N-oxides (7-11) and pyridine-N-oxide (12) using diisopropylamine/TEA as base in very good yields (Scheme 8).

2-picoline-N-oxide (7) and lutidine-N-oxide (8) when reacted with triphosgene in the presence of diisopropylamine at -20 °C gave 2-chloromethylpyridine (13) in 90% yield and 2-chloromethyl-3-methylpyridine (14) in 80% yield respectively. Similarly collidine-N-oxide (9) gave two products namely 2-chloromethyl-4, 6-dimethylpyridine (15) in 65% yield.
(82% selectivity) and 4-chloromethyl-2,6-dimethylpyridine (16) in 15% yield (18% selectivity). 4-picoline-N-oxide (10) also gave two products, 4-chloromethylpyridine (17) in 61% yield by side chain chlorination (80% selectivity; isolated as hydrochloride salt) and 2-chloro-4-methylpyridine (18) in 14% yield by ring chlorination (20% selectivity). Similarly, Pyridine-N-oxide (12) exclusively gave ring chlorinated 2-chloropyridine (21) in 80% yield. 3-Picoline-N-oxide (11) under similar conditions gave two possible isomeric products 2-chloro-5-methyl pyridine (19) in 70% yield (87% selectivity) and 2-chloro-3-methyl pyridine (20) in 10% yield (13% selectivity).

Table 1 clearly indicates the scope, generality and selectivity towards the formation of side chain (vs) ring chlorinated products.

Scheme 8

3.4 Results and discussion

2-Chloromethyl pyridine has been prepared by the direct chlorination by using chlorine gas of α-picoline but the yields were low due to formation of large amount of di and tri chloromethylpyridines, in another route 2-chloropyridine can be synthesized by using 2-picoline N-oxide using POCl₃ by this method yields are moderate but waste disposal are high,
tedious work up procedure, the yields with this reagent is 90%, selectivity is 98%, time period is only 25 min at 40 °C.

In another paper reported that the same conditions are followed except increasing the time period from 25 min to 1hr, and mole ratio used is stoichiometry even though the yields are 90 % and selectivity was 98 %.

4-Chloro-2-chloromethylpyridine was synthesized from 2-methyl pyridine -N-oxide by three-step process i.e. nitration to yield the 4-nitro derivative followed by treatment with conc. HCl to give the 4-chloro product in 84 % yield. The side chain methyl group was chlorinated in 16 % yield by using P-toluene sulphonylchloride.

By using diphosgene/triphosgene, 80 % of 4-chloromethylpyridine was obtained at -40 °C with easy work up procedure and the ring chlorination is 20% giving 2-chloro-4-methylpyridine.

For example pyridine-N-oxide (1) using diphosgene is a chlorinating agent in one step at -40 °C and by using diisopropylamine as base to get the 2-chloromethyl pyridine (7) with 92 % yield by changing the base from diisopropylamine with triethylamine also getting yield ~90 % only. The same procedure is adopted to synthesize compound (7) using triphosgene as chlorinating agent and the yields are some what less compare with diphosgene. This may be due to liberation of one mole of phosgene with the expense of one mole of triphosgene along with generated CCl₄ which reduce the reaction progress where as one mole of diphosgene liberates 2 moles of phosgene. Diphosgene is more efficient chlorinating agent than the triphosgene but the simple handling and low toxicity of the triphosgene makes it better chlorinating agent than the diphosgene. Scheme 2, Scheme 3.
Chapter III

Chloromethylpyridines and Chloropyridines...

Table 1. Synthesis of chloromethylpyridines and chloropyridines.

<table>
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<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Temperature (°C)</th>
<th>%Y in presence of DIPA</th>
<th>%Y in presence of TEA</th>
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<td></td>
<td>DP</td>
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<td>8</td>
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<td>(14) NCH3CH2Cl</td>
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<td></td>
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<td>-20</td>
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<td>9</td>
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<td>DP</td>
<td>(15) NCH3C1H2Cl  + (16) NCH3C1H3</td>
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<td>78</td>
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Note: All the products were well characterized by its 1H NMR and GC/GCMS. A, Substrate; B, reagent; C, product; T, temperature; y, yield; DIPA, diisopropyl-amine; TEA, triethylamine; DP, diphosgene; TP, triphosgene.

3.5 Conclusions:

The simple handling and low toxicity easy disposable nature of the triphosgene makes it better chlorinating agent. Diphosgene and triphosgene in the presence of amines were found to
be an excellent chlorinating agent with high selectivity for the preparation of chloromethylpyridines and chloropyridines from picoline-N-oxides and pyridine-N-oxides respectively. In summary, the method reported is very mild, efficient reagent with high selectivity.

3.6 Experimental procedure:

A stock solution of triphosgene (2.97 g, 30 mmol) in dichloromethane (10 mL) was prepared, of which 1 mL was added dropwise to 2-methylpyridine-N-oxide (7, 1.63 g, 15 mmol) in dichloromethane (15 mL) at -20 °C, after 15 min the remaining solution was added dropwise along with diisopropylamine (3.03 g, 30 mmol) in dichloromethane (10 mL) over a period of 1 hr at -20 °C. The contents were slowly brought to room temperature and stirred for another 45 min. The mass was quenched with water (10 mL), stirred for 30 min and the organic layer was separated. The aqueous layer was basified with NaOH solution (pH 7-8) and extracted with dichloromethane (2 x 50 mL). The organic layer was dried over Na₂SO₄ and the solvent removed under reduced pressure to give 13 (1.75 g) in 90 % yield. The same procedure is adopted for remaining all the compounds; all these compounds were well characterized by ¹H NMR, GCMS.

3.7 Characterization data

2-chloromethylpyridine (13):

Yield : 92 %
State : liquid. b.p. 73-76 °C
¹H NMR (CDCl₃) : δ 4.7 (s, 2H), 7.3 (t, 1H), 7.55 (d, 1H), 7.95 (t, 1H), 8.6 (d, 1H).
Chapter III  

Chloromethylpyridines and Chloropyridines...

**2-chloromethyl-3-methylpyridine (14):**

Yield : 85 %  
State : liquid. b.p.: 59-61 °C  
$^1$H NMR (CDCl$_3$) : δ 2.4 (s, 3H), 4.62 (s, 2H), 7.15 (t, 1H), 7.42 (d, 1H), 8.39 (d, 1H).  
EI-MS (m/z) : 141(M$^+$)(30), 120 (100), 106 (25), 93 (30), 77 (65), 41 (80).

**2-chloromethyl-4,6-dimethylpyridine (15):**

Yield : 80 %  
State : liquid. b.p.: 69-70 °C  
$^1$H NMR (CDCl$_3$) : δ 2.3 (s, 3H), 2.45 (s, 3H), 4.55 (s, 2H), 6.85 (s, 1H), 7.05 (s, 1H),  
EI-MS (m/z) : 155(M$^+$)(20), 149 (30), 141 (40), 100 (100), 72 (75).

**4-chloromethyl-2,6-dimethylpyridine (16):**

Yield : 80%  
$^1$H NMR (CDCl$_3$) : δ 2.45 (s, 6H), 4.35 (s, 2H), 6.85 (s, 2H).  
EI-MS (m/z) : 155(M$^+$)(100), 120 (75), 77 (45), 51 (25).

**2-chloromethylpyridine (17):**

Yield : 85 %  
State : liquid. b.p.: 73-76 °C  
$^1$H NMR (CDCl$_3$) : δ 4.7 (s, 2H), 7.3 (d, 2H), 8.6 (d, 2H).  
EI-MS (m/z) : 127(M$^+$)(15), 110 (100), 72 (25), 39 (30).

**2-chloro-4-methylpyridine (18):**

Yield : 20 %  
State : liquid. b.p.: 97-99 °C
### Chapter III

**Chloromethylpyridines and Chloropyridines...**

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<th>Yield</th>
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<td>2-chloro-3-methylpyridine (20)</td>
<td>13%</td>
<td>liquid. b.p.: 192-193 °C</td>
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<td>2-chloropyridine (21)</td>
<td>80%</td>
<td>liquid. b.p.: 170 °C</td>
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<td>EI-MS (m/z)</td>
<td>127(M(^+))(100), 92 (60), 65 (50).</td>
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74
3.8 References:


Chapter III
Chloromethylpyridines and Chloropyridines...


Figure 1: $^1$H NMR Spectrum of 2-chloromethylpyridine (13)
Figure 2: EI-Mass Spectrum of 2-chloromethylpyridine (13)
Figure 3: $^1$H NMR Spectrum of 2-chloromethyl-3-methylpyridine (14)
Figure 4: EI-Mass Spectrum of 2-chloromethyl-3-methylpyridine (14)
Figure 5: $^1$H NMR Spectrum of 2-chloromethyl-4,6-dimethylpyridine (15)
Figure 6: EI-Mass Spectrum of 2-chloroethyl-4,6-dimethylpyridine (15)
Figure 8: EI-Mass Spectrum of 4-chloromethyl-2, 6-dimethylpyridine (16)
Figure 17: $^1$H NMR Spectrum of 4-chloromethylpyridine (17)
Figure 18: EI-Mass Spectrum of 4-chloromethylpyridine (17)
Figure 9: $^1$H NMR Spectrum of 2-chloro-4-methylpyridine (18)
Figure 10: EI-Mass Spectrum of 2-chloro-4-methylpyridine (18)
Figure 11: $^1$H NMR Spectrum of 2-chloro-3-methylpyridine (19)
Figure 12: EI-Mass Spectrum of 2-chloro-5-methylpyridine (19)
Figure 13: $^1$H NMR Spectrum of 2-chloro-3-methylpyridine (20)
Figure 14: EI-Mass Spectrum of 2-chloro-3-methylpyridine (20)
Figure 15: $^1$H NMR Spectrum of 2-chloropyridine (21)