CHAPTER-V

PART-A:

Synthesis of
N'-Carbamoyl-N-[(6-chloropyridin-3-yl)methyl]ethanimidamide

PART-B:

Synthesis of
N'-[(Aminomethyl)]-N-[(6-chloropyridin-3-yl)methyl]-N-methyl
ethanimidamide
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5.1 Introduction

Acetamiprid, N-[(6-chloro-3-pyridyl)methyl]-N’-cyano-N-methylacetamidine, is a novel insecticide developed by Nippon Soda Co., Ltd to control various noxious insects in agriculture. Mode-of-action studies of acetamiprid suggested that the nicotinic acetylcholine receptor (nAChR) is its primary binding site, as with neonicotinoid insecticides such as imidacloprid. The N-cyanoacetamidine structure of acetamiprid is unique and characteristic since most known neonicotinoids have nitromethylene or nitroimine structures.\(^1\) Acetamiprid has been already well documented. X-ray analysis revealed that the E-geometry along with the imine double bond and syn-relation between the two methyl groups.\(^2\)

Acetamiprid, contains cyanoimine functional group, less persistent in acidic medium, while at pH 9.0, first significant changes appeared after the 30 days.\(^3\) Low efficacy of acetamiprid in soil application can be attributed to the fact that acetamiprid could be easily degraded and the partial degraded inter-metabolite demethylated acetamiprid (ACE-dm) remained less bioactive. Therefore, N-demethylation of acetamiprid by some soil bacteria such as \textit{S. maltophilia} might be able to metabolize acetamiprid to ACE-dm. The involvement of P450 in the N-demethylation of some drugs has been reported in human cells.\(^4\) N-demethylation as ACE-dm, the most prominent metabolite of those analyzed, cyano hydrolysis to ACE-NCONH\(_2\). ACE-dm underwent similar pathways to acetamiprid to yield ACE-dm-NCONH\(_2\).\(^5\) Metabolic study on mice observed that acetamiprid and ACE-dm in brain, liver, plasma and urine, while ACE-dm-NCONH\(_2\) was observed in urine only.\(^6,7\) Here, we reported the chemical pathway of hydrolysis of acetamiprid in alkaline condition to get a similar product as reported on natural metabolites of acetamiprid by previous workers.
5.2 Summary of the work

Acetamiprid is hydrolyzed by using NaOH to get amide derivative of acetamiprid which was further demethylated (Scheme-1). The hydrolysis product of the starting compound has been confirmed on the basis of IR and PMR spectral data.

5.3 Experimental procedure

N-[(6-Chloropyridin-3-yl)methyl]-N'-cyano-N-methylethanimidamide (Acetamiprid) (1): Commercial available acetamiprid is further purified by centrifugation method in water and again recrystallized in methanol to get a highly purified acetamiprid for further reaction.

IR (KBr) $\nu_{\text{max}}$: 3079, 3049, 2987, 2938, 2175, 1572 cm$^{-1}$.  

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.48(s, CH$_3$), 3.10(s, CH$_3$), 4.03(s, CH$_2$), 7.36(d, J=7.5 Hz, PyH), 7.68(dd, $J_1$=8.2 Hz, $J_2$=2.5 Hz, PyH), 8.32(s, PyH) ppm.

N'-Carbamoyl-N-[(6-chloropyridin-3-yl)methyl]ethanimidamide (ACE-dmNCONH$_2$) (2): The solution of acetamiprid (4.44 gm, 0.02 mole) in 30 ml of 6N NaOH and ethanol refluxed for 13 hrs., cooled and neutralized with H$_2$SO$_4$, to get a white solid which was filtered and dried. Yield 70%.

IR (KBr) $\nu_{\text{max}}$: 3460, 3423, 3354, 3142, 2871, 2931, 1663, 1567 cm$^{-1}$.  

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.88(s, CH$_3$), 4.52(s, CH$_2$), 4.56(s, NH$_2$), 7.30(d, J=7.5 Hz, PyH), 7.64(dd, J=8.2 Hz, J=2.5 Hz, PyH), 8.28(s, PyH), m/z.

![Scheme-1](image-url)
5.4 Conclusions

The process of alkaline hydrolysis of acetamiprid has been monitored in 6N NaOH. It was observed that N-demethylation occurred followed by the hydrolysis of cynogroup to the corresponding amide. This observation is in conformity with the earlier reported metabolites of hydrolysis of acetamiprid $^{6,7}$ACE-dm NCONH$_2$. 
5.5 References

Fig. No. 1. IR spectrum of the compound (1).
Fig. No. 2. $^1$HNMR spectrum of the compound (2).
Fig. No. 3. IR spectrum of the compound (2).
PART-B:

Synthesis of

N'-(Aminomethyl)-N-[(6-chloropyridin-3-yl)methyl]-N-methyl
ethanimidamide
PART-B

Synthesis of N’-(Aminomethyl)-N-[(6-chloropyridin-3-yl)methyl]-N-methylethanimidamide

5.1 Introduction

Lithium aluminium hydride has been successfully employed for the reduction of aliphatic and aromatic nitrile as well as several cyanides. Best results are obtained when the reduction is carried out with hydrogen and platinum or palladium catalyst in the presence of mineral acid. With the lower molecular weight compounds, the rise in the yield of sodium cyanide parallels the decrease in the yield of primary amine. With the higher molecular weight secondary and tertiary cyanides the yield of amine corresponds quite well to those obtained from the lower secondary and tertiary cyanides, but the yields of the sodium cyanide are lower. The low yields of this latter product (and possibly the primary amines) are due to incomplete reduction of the cyanide. When the cyanide group is attached to a carbon which carries a phenyl group, its halogen-like behavior demonstrated by the high yield of sodium cyanide obtained from its by reduction with sodium and alcohol.\(^1\) Diisopropylaminoborane \([\text{BH}_2N(i\text{Pr})_2]\) in the presence of a catalytic amount of lithium borohydride \((\text{LiBH}_4)\) reduces a large variety of aliphatic and aromatic nitriles in an excellent yields.\(^2\) Benzyl cyanide has also been successfully reduced using Raney nickel under hydrogen atmosphere.\(^3\) The reported generic reduction protocol for nitriles employing catalytic quantities of nickel (II) chloride with an excess of sodium borohydride facilitate the formation of Boc (t-butyl dicarbonate) protected amines.\(^4\) The reduction of cyano group in aromatic nitriles to primary amines gives high yields with nickel boride at ambient temperature. The reductions are very rapid and are complete in 5 min.\(^5\) Ni(II) salts have drawn wide attention in the modification of sodium borohydride reactivity. Nickel boride has been reported as a catalyst in the reduction of nitriles under hydrogen atmosphere.\(^6\) A new and efficient method of synthesizing primary amines from their corresponding nitriles with KBH\(_4\) in dry ethanol catalyzed by Raney Ni has been discovered.\(^7\) In 2002, Gowda et al \(^8\) found that using Raney Ni / \(\text{N}_2\text{H}_4 / \text{HCOOH}\) could transform nitriles to the corresponding primary amines with the70% yield. Here, we have
reported the reduction of acetamiprid having cyno group to their corresponding amine by sodium in absolute alcohol.\textsuperscript{3}

5.2 Summery of the work

The reduction of acetamiprid by sodium and absolute alcohol has been achieved successfully with an excellent yield of the product. The synthesized compound has been well characterized by spectral data.

5.3 Experimental procedure

$\text{N'-(Aminomethyl)-N-[(6-chloropyridin-3-yl)methyl]-N-methylethanimidamide}$ (2) : To the solution of acetamiprid (2.22 gm., 0.01 mole) in an absolute ethanol, freshly cut dry sodium metal (1.10 gm., 0.05 mole), was added and the reaction mixture refluxed for 5 hrs. and the solvent removed under reduced pressure to yield an amine, yield 60%.

$\text{IR (KBr)} \nu_{\text{max}}$: 3422, 2925, 2853, 1602 cm\textsuperscript{-1}. \hspace{1cm} (\text{Fig. No. 1})

\begin{equation}
\begin{array}{c}
\text{Cl} \quad \text{N} \\
\text{N} \quad \text{CN} \\
\text{Cl} \quad \text{N} \\
\text{N} \quad \text{CH}_2\text{-NH}_2 \\
\end{array}
\end{equation}

\text{Scheme-1}

5.4 Conclusions

The cyno group of acetamiprid is easily reduced to amine by sodium in absolute ethanol. This reduced compound may further be utilized for the synthesis of useful derivatives having a value as a pesticide.
5.5 References
