

CHAPTER – IV

AN ELEGANT SYNTHESIS OF IMIDAZO[1,2- a] PYRIDINE -3-ACETONITRILE DERIVATIVES AND SIMPLIFIED PROCESS FOR THE SYNTHESIS OF ZOLPIDEM

CHAPTER – IV

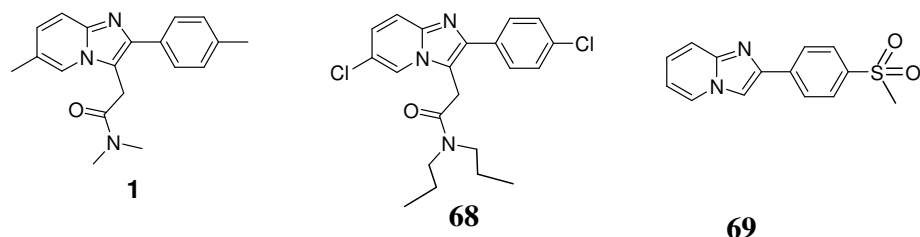
AN ELEGANT SYNTHESIS OF IMIDAZO[1,2-a]PYRIDINE -3- ACETONITRILE DERIVATIVES AND SIMPLIFIED PROCESS FOR THE SYNTHESIS OF ZOLPIDEM

4.1 INTRODUCTION:

Imidazo[1,2-a]pyridines have received considerable attention in medical sciences and pharmaceutical industry due to their biological and pharmacological activities¹. Imidazo[1,2-a]pyridines exhibit a wide range of biological activities²⁻⁴ such as hypnotic⁵, sedative, anti-inflammatory⁶, anti tumor⁷, calcium channel blocker, anti microbial⁸, anti tubercular, CNS depressant, anti thyroid, anxi selective and many other therapeutic activities. Several imidazo[1,2-a]pyridine derivatives are currently in the market including hypnotic drug

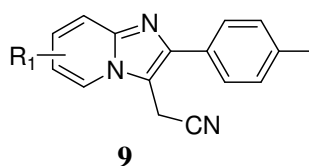
Zolpidem (**1**), non sedative anxiolytic drug Alpidem (**68**) and an anti ulcer agent Zolmidine (**69**).

Figure 1



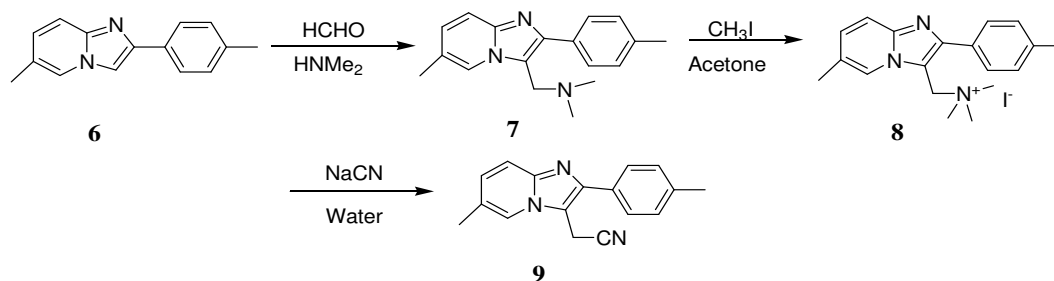
Zolpidem (**1**), N,N-Dimethyl-2-(6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-yl)acetamide, is used for the short term treatment of insomnia and some brain disorders. It is available in the market as its tartrate salt. It potentiates gamma amino butyric acid (GABA), an inhibitory neuro transmitter, by binding to benzodiazepine receptors located on the gamma amino butyric acid receptors. Although its hypnotic effects are similar to those drugs of the benzodiazepine class, it is molecularly distinct from benzodiazepines.

[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-yl]acetonitrile **9** is a key intermediate for the preparation of anti hypnotic drug Zolpidem. In the literature, several synthetic methods have been described for the preparation of 3-cyanomethyl imidazo[1,2-a]pyridine derivative.



4.2 LITERATURE BACKGROUND

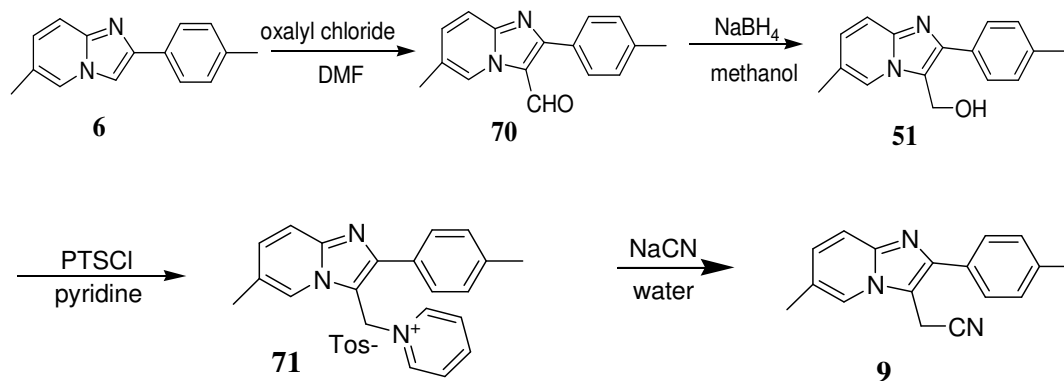
Jean-pierre Kaplan and Pasaal George et al⁹ reported synthesis of cyanomethyl derivative **9** by the reaction of formaldehyde and dimethylamine in acetic acid to produce Mannich base **7**. Mannich base **7** was treated with methyl iodide in acetone to produce the quaternary ammonium salt **8**, which was further reacted with NaCN to yield the corresponding nitrile derivative **9** (**Scheme 4.1**):



(Scheme 4.1)

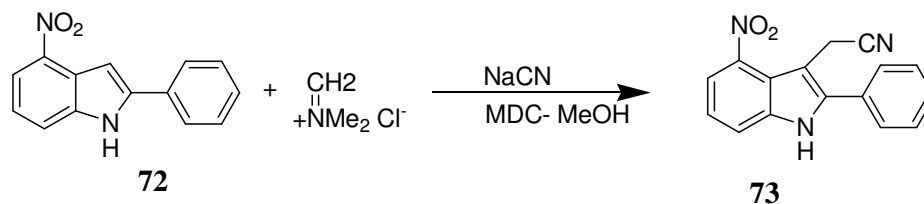
Jean Michel and Bernardon et al¹⁰ reported the preparation of cyanomethyl derivative **9** by the formylation process. In this approach (**Scheme 4.2**), 2-(4-methylphenyl)-6-methylimidazo[1,2-a]pyridine **6** was treated with oxalylchloride and dimethylformamide to get the formyl derivative of 3-formyl-2-(4-methylphenyl)-6-methylimidazo[1,2-a]pyridine **70**, which on reduction with sodium borohydride gave the corresponding alcohol derivative [6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-yl]methanol **51**. This alcohol, on treatment with p-toluenesulfonylchloride in pyridine, produced pyridinium tosylate salt **71**, which on further treatment with sodium

cyanide gave the cyanomethyl derivative of imidazo[1,2-a]pyridine **9**. However, this process involved the usage of toxic chemicals like oxalyl chloride, sodiumborohydride and required more number of steps resulting in lower yield. Hence it was unsuitable for large scale preparation.



(Scheme 4.2)

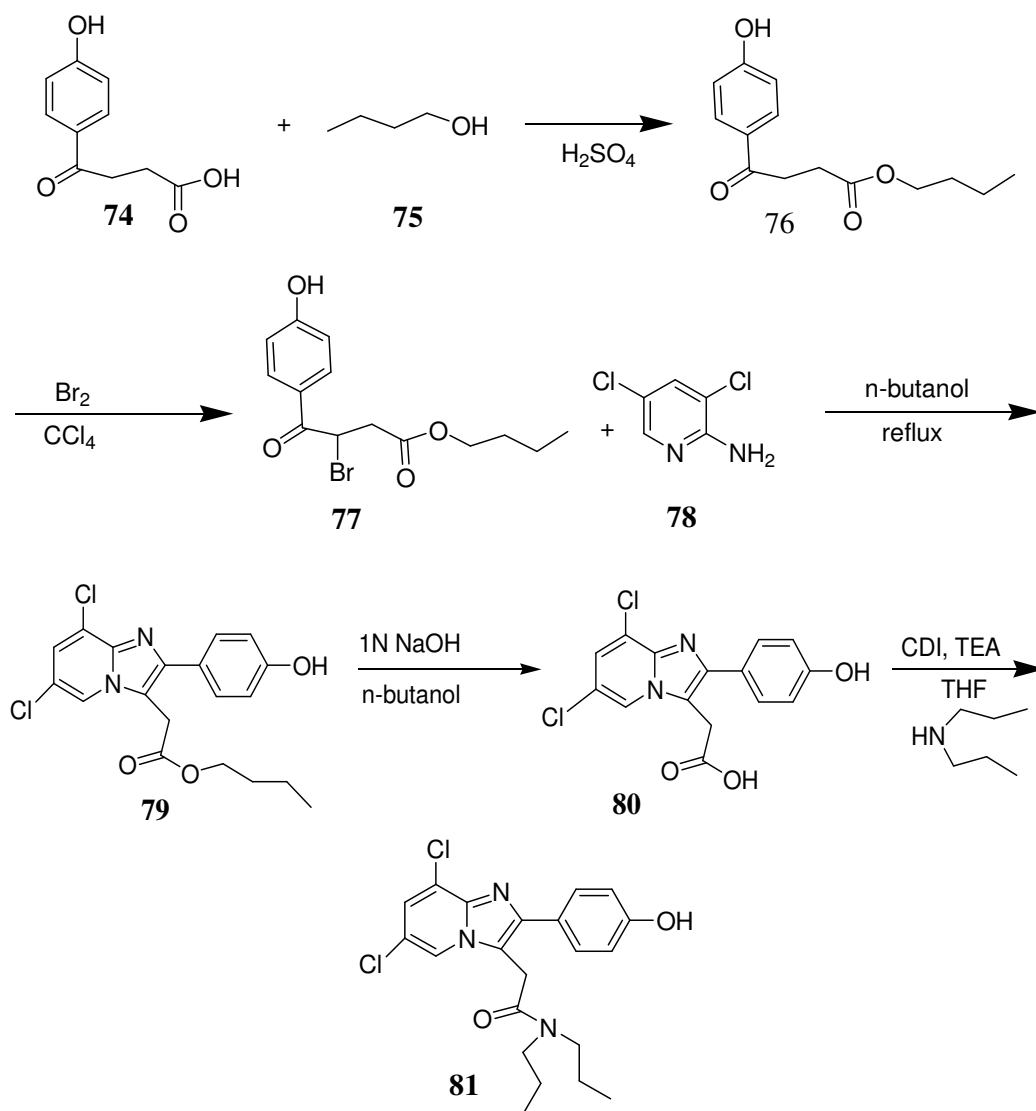
A.P . Kozikowski and D. Ma et al¹¹ reported, the synthesis of 2-(4-nitro-2-phenyl-1H-indole-3-yl)acetonitrile **73**, by the reaction of 4-nitro-2-phenyl-1H-indole **72** with Mannich salt in MDC and methanol, Containing sodiumcyanide to produce **73**(Scheme 4.3).



(Scheme 4.3)

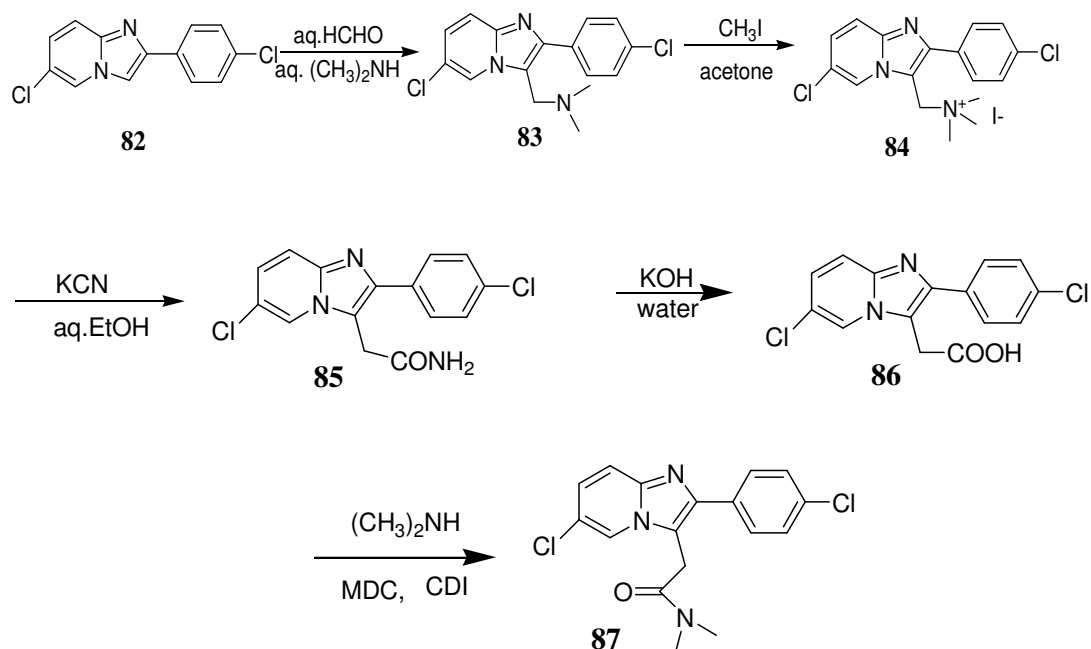
Nunzio Denora, and Velentino et al¹² reported, the synthesis of 2-(6,8-dichloro-2(4-hydroxyphenyl)imidazo[1,2-a]pyridine-3-yl)-N,N-dipropylacetate **81**, by the reaction of 4-(4-hydroxyphenyl)-4-oxobutanoic acid **74** with n-butanol **75** in H₂SO₄ to produce butyl

4-(4-hydroxyphenyl)-4-oxobutanoate **76**. The compound **76** was treated with bromine in CCl_4 to produce butyl 3-bromo-4-(4-hydroxyphenyl)-4-oxobutanoate **77**. The compound **77** condensation with 3,5-dichloropyridin-2-amine **78** in n-butanol to produce butyl 2-(8-dichloro-2-hydroxyphenyl)imidazo[1,2-a]pyridine-3-yl)acetate **79**, which was hydrolyzed in n-butanol containing 1N NaOH to produce acid derivative **80**. The acid derivative **80** on treatment with amine in THF containing CDI to produce corresponding amide **81** (Scheme 4.4)



(Scheme 4.4)

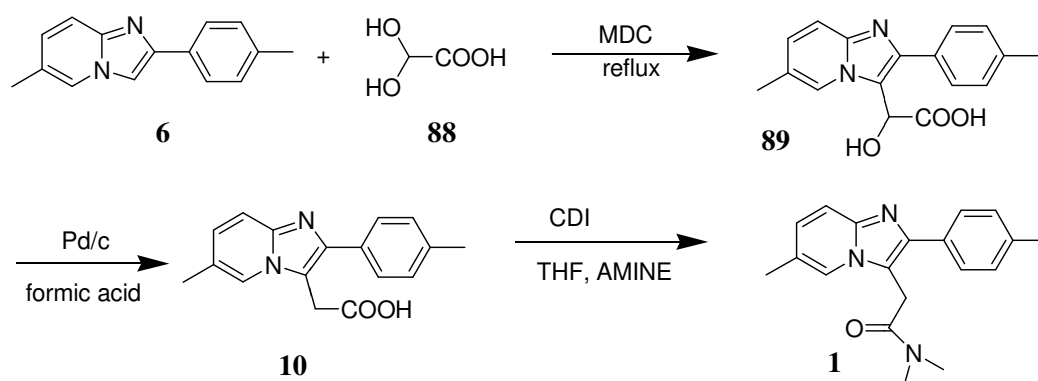
Jerzy Lange et al¹³ reported, the synthesis of 2-(6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl)-N,N-dimethylacetamide **87**, by the reaction of 6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine **82** with aq.dimethylamine and aq.formaldehyde in presence of acetic acid to produce Mannich Base **83**. The compound **83**, was treated with methyl iodide in acetone to produce **84**, which was further treated KCN to yield the corresponding amide derivative **85**. The amide derivative **85** was hydrolyzed with KOH in water to give 2-(6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl) acetic acid **86**. The compound **86**, on treatment with amine to yield the corresponding amide **87** (Scheme 4.5)



(Scheme 4.5)

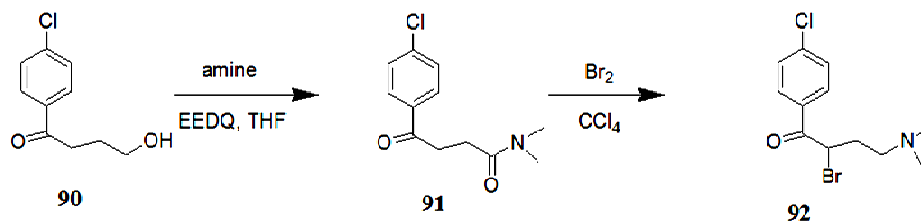
Gerrit Jan Bouke Ettema and Jacobus Maria Lemmens et al¹⁴ reported, the synthesis of Zolpidem **1**, by the reaction of 6-methyl -

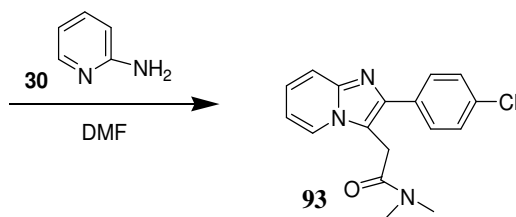
2-*p*-(tolyl)imidazo[1,2-*a*]pyridine **6**, with 2,2-dihydroxyacetic acid **88** in MDC to produce 2-hydroxy-2-(6-methyl-2-*p*-(tolyl)imidazo[1,2-*a*]pyridin-3-yl)acetic acid **89**. The compound **89** was dehydroxylated in formic acid containing Pd/C as a catalyst treated to produce acid derivative **10**. The acid derivative **10** was aminated with dimethylamine to give the corresponding amide **1** (Scheme 4.6).



(Scheme 4.6)

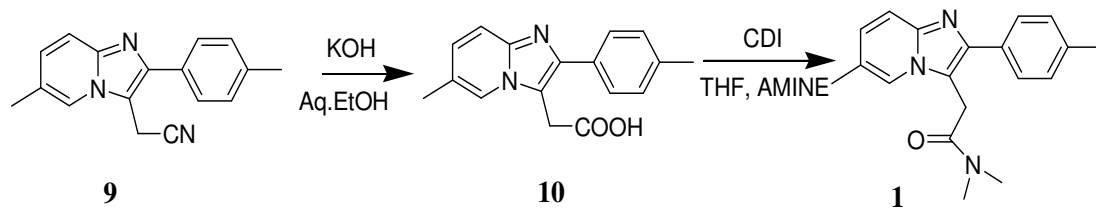
Giuseppe Trapani and Valentino et al¹⁵ reported, the synthesis of 2-(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)-*N,N*-dimethylacetamide **93**, by the reaction of 1-(4-chlorophenyl)-4-hydroxybutan-1-one **90** with dimethylamine in THF to produce 4-(4-chlorophenyl)-*N,N*-oxobutanamide **91**. The compound **91** was brominated with Br₂ in CCl₄ to produce **92**, which was condensation with 2-aminopyridine **30** in DMF produced **93** (Scheme 4.7).





(Scheme 4.7)

Zolpidem disclosed in European patent No.50563 equivalent to US pat. No. 4382938 in year 1984 was assigned to synthelab⁹. There after several authors published the processes for the preparation of zolpidem. The inventors reported that the procedure for the preparation of 3-cyanomethyl derivative of imidazo[1,2-a]pyridine **9**, as depicted in **(scheme4.1)**. The cyano compound, on alkaline hydrolysis, yielded a pyridine aceticacid **10**, [6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]aceticacid, commonly known as zolpidic acid. The acid derivative was reacted with carbonyldiimidazole, followed by amidation with anhydrous dimethylamine to give zolpidem as depicted in **(scheme 4.8)**. This process suffers from several disadvantages such as i) use of volatile and expensive methyl iodide ii) use of carbonyl diimidazole (CDI), which is a highly moisture sensitive and sometimes even a small amount of moisture restricted the proceeding of the reaction iii) by using CDI larger amounts of imidazole is formed as by product and difficult to removal from the reaction mass iv) need to use anhydrous dimethylamine gas v) more number of steps and lower overall yield.



(Scheme 4.8)

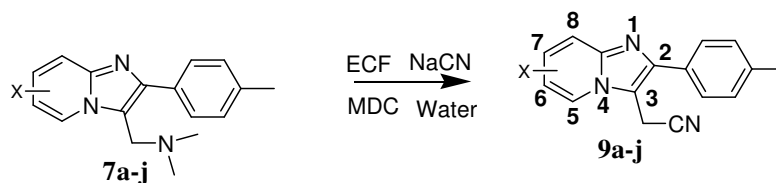
4.3 PRESENT WORK:

All known synthesis of zolpidem and its key intermediate 3-cyanomethyl derivative used either reagents commercially difficult to access, toxic to handle or products with poor purity that should undergo repeated purification procedures. Therefore it would be desirable and paramount importance to have an alternate method for the preparation of 3-cyanomethyl derivative and zolpidem avoiding the use of the expensive and highly toxic methyl iodide, sodium borohydride and CDI and employing inexpensive, readily available and easy to handle reagents. It would also be desirable to have a process that can be readily scaled up and which does not require a special purification step to obtain pure zolpidem.

4.4 RESULTS AND DISCUSSION:

In view of the above drawbacks, we focused our attention to circumvent the use of volatile, low boiling and expensive methyl iodide and make the process for the preparation of [6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetonitrile **9**, by a simple and scalable process for industrial application. We have examined the use of ethylchloroformate as the reagent for the formation of quaternary salt in lieu of methyl iodide. 3-(N,N-dimethylaminomethyl)-2-(4-methylphenyl)-6-methylimidazo[1,2-a]pyridine **7** was treated with ethylchloroformate in dichloromethane solvent and within a few minutes the starting material was absent in Thin Layer chromatography. This prompted us to study the reaction in detail. The

reaction of Mannich base **7** with 1.2 molar equivalents of ethylchloroformate in dichloromethane for 30 min, at 0-5°C, followed by evaporation of the solvent yielded a solid. The solid was dissolved in water, basified and treated with sodium cyanide to produce the key 3-acetonitrile intermediate **9** in good yield and purity. With a view to extend this protocol and find the efficacy of ethylchloroformate for the formation of cyanomethyl derivatives of imidazopyridines, various Mannich bases of substituted imidazo[1,2-a]pyridines derivatives were treated with ethylchloroformate, followed by sodium cyanide under similar conditions (**Scheme 4.10**) to obtain the respective products as expected. The results are given the **Table 4.1**.



(Scheme 4.10)

Table 4.1: Various 3-Cyanomethyl derivatives of imidazo[1,2-a]pyridines

Entry	Product	X	Time	Yield
1	9a	6-CH ₃	3h	85%
2	9b	6-Cl	3h	82%
3	9c	6-Br	3.5h	84%
4	9d	7-CH ₃	3h	83%
5	9e	7-Cl	3.5h	78%
6	9f	7-Br	4h	80%
7	9g	6-Br-7-CH ₃	4h	76%
8	9h	6-Cl-7-CH ₃	4h	80%
9	9i	5-CH ₃	4h	74%
10	9j	H	4h	76%

We have also evaluated the process for the preparation of **9**, with variety of alkylchloroformates. Ethylchloroformate is replaced with other alkylchloroformates and the results shown in Table **4.2**. Although reactions were successful with all other alkylchloroformates, the yields reduced using other chloroformates were very less and it was decided to use ethylchloroformate as the reagent.

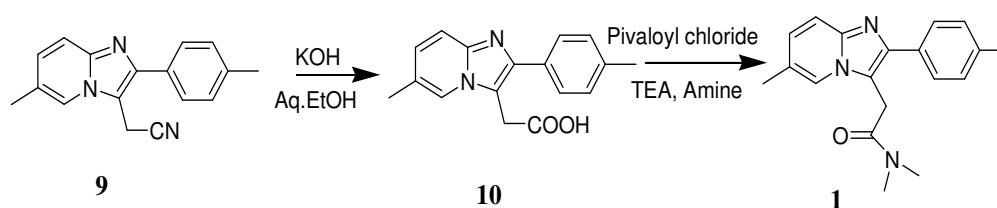
Table 4.2: Preparation of 3-Cyanomethyl derivative of imidazo[1,2-a]pyridine 9 with alkylchloroformates

Entry	Alkylchloroformate	Time	Yield
1	Methylchloroformate	4h	48.0%
2	Ethylchloroformate	3h	85.0%
3	Isopropylchloroformate	4h	37.5%
4	Isobutylchloroformate	4h	42.5%
5	Phenylchloroformate	4h	32.0%
6	Benzylchloroformate	4h	74.5%

In addition to new method to produce the key intermediate cyano derivative **9**, we have also studied the hydrolysis of **9**, in acidic medium. So far, all the reports used alkaline hydrolysis for the hydrolysis **9**, to zolpidic acid **10**, but it took long hours at higher temperatures. Our attempts to use conc. Hydrochloric acid in aqueous medium and acetic acid medium did not give desired yield and quality. The results using 10% and 20% aqueous sulfuric acid solution, proceeded slowly to give Zolpidic acid. An attempt using 50% sulfuric acid solution successfully completed hydrolysis within two hours and produced good results.

After successful cyanation and hydrolysis, the focus shifted to eliminate the use of CDI in the amidation step. Thionylchloride and phosphorous pentachloride¹⁶ were tried for the formation of

acidchloride followed by passing dimethylamine gas to produce the required product. Since using dimethylamine gas was cumbersome and due to unsatisfactory results, this process of amidation was discontinued. We discovered that zolpidic acid **10**, on treatment with pivaloyl chloride in the presence of triethylamine produced mixed anhydride, which on treatment with aqueous 40% dimethylamine solution produced zolpidem in good yield and purity. The schematic presentation for the preparation of zolpidem is shown in **(Scheme 4.11)**.



(Scheme 4.11).

CONCLUSION:

In conclusion we have formulated and developed a new method for the synthesis of the key intermediate of zolpidem namely, 6-(methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**9**). The present synthetic method is generalized and applied for the synthesis of various acetonitrile derivatives of imidazo[1,2-a]pyridines **9a-j**. This approach provided an efficient, cost effective and simple synthetic method for the preparation of insomnia drug zolpidem avoiding expensive and unstable reagents methyl iodide and CDI respectively.

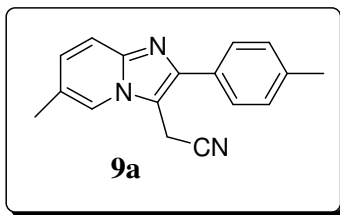
The overall yield of Zolpidem has increased from reported 40% to 65% with this improved process.

4.5: EXPERIMENTAL SECTION:

General procedure for the preparation of cyanomethyl derivatives of imidazo[1,2-a]pyridines (9 a-j).

To a solution of dimethylaminomethyl derivatives of Imidazo[1,2-a]pyridine (**7a-j**) in dichloromethane, was added ethylchloroformate under cooling. The reaction mixture was stirred for 30 minutes and solvent was distilled off under reduced pressure to obtain a solid. The solid was dissolved in water and the pH of the solution was adjusted to 8.0 using sodiumhydroxide solution. To this aqueous solution, sodium cyanide was added and the mixture was stirred at 50-55°C for 3-4 hours. After cooling the reaction mixture to room temperature, it was extracted with chloroform and the organic layer was washed with water and brine. Then it dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude compound was stirred with methanol and filtered to obtain a pure product.

9a: [6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetonitrile.



Description : off-white solid.

HPLC Purity: 99.6%.

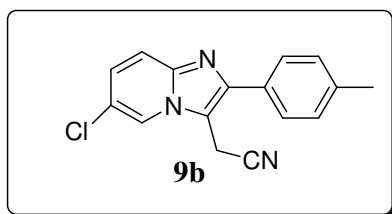
IR (IN KBr): 2250.2 cm^{-1}

^1H NMR (CDCl_3/TMS): δ 2.42 (s, 6H), 4.11 (s, 2H), 7.16 (dd, $J = 1.4$ Hz, $J = 9.1$ Hz, 1H), 7.31 (d, $J = 7.9$ Hz, 2H), 7.57 (d, $J = 8.1$ Hz, 2H), 7.60 (d, $J = 9.4$ Hz, 1H), 7.80 (s, 1H).

^{13}C NMR (CDCl_3/TMS): δ 13.8, 18.3, 21.2, 107.0, 115.1, 117.1, 120.4, 123.0, 128.2, 129.5, 130.3, 138.2, 144.3, 144.9.

ESI MS: 262.2 (M+1).

9b: [6-Chloro-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetonitrile.



Description : off-white solid.

HPLC Purity: 99.2%.

IR (IN KBr): 2248.2 cm^{-1} .

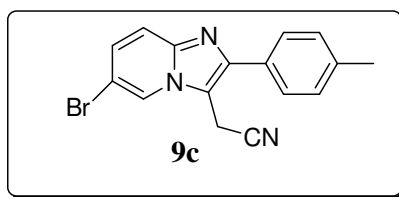
¹H NMR (CDCl₃/TMS): δ 2.42 (s, 3H), 4.12 (s, 2H), 7.28 (dd, *J* = 1.7 Hz, *J* = 9.6 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 9.5 Hz, 1H), 8.08 (s, 1H).

¹³C NMR (CDCl₃/TMS): δ 13.9, 21.3, 108.0, 114.6, 118.2, 120.7, 121.6, 126.6, 128.3, 129.7, 138.8, 143.7, 146.2.

ESI MS: 282.4(M+1).

9c: [6-Bromo-2-(4-methylphenyl) imidazo[1,2-a]pyridin-3-yl]

acetonitrile.



Description : off-white solid.

HPLC Purity: 99.0%.

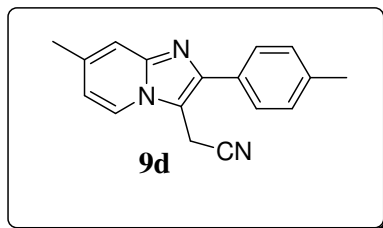
IR (IN KBr): 2248.8 cm⁻¹.

¹H NMR (CDCl₃/TMS): δ 2.43 (s, 3H), 4.14 (s, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.40 (dd, *J* = 1.6 Hz, *J* = 9.5 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 9.5 Hz, 1H), 8.19 (s, 1H).

¹³C NMR (CDCl₃/TMS): δ 13.6, 21.2, 107.1, 110.3, 117.1, 118.3, 125.0, 128.1, 128.6, 129.7, 130.5, 138.0, 143.1, 144.2.

ESI MS: 326.2 (M+1), 328.2 (M+3).

9d: [7-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]
acetonitrile.



Description : off-white solid.

HPLC Purity: 99.1%.

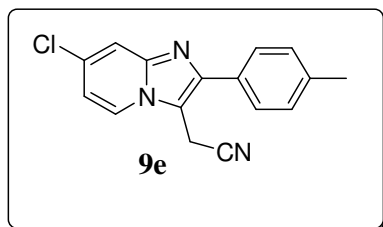
IR (IN KBr): 2246.9 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ 2.41 (s, 3H), 2.44 (s, 3H), 4.11 (s, 2H), 6.80 (dd, $J = 1.5$ Hz, $J = 6.9$ Hz, 1H), 7.30 (d, $J = 7.9$ Hz, 2H), 7.44 (s, 1H), 7.57 (d, $J = 8.0$ Hz, 2H), 7.91 (s, 1H).

^{13}C NMR (CDCl_3/TMS): δ 13.6, 21.1, 106.6, 115.1, 115.5, 116.0, 121.8, 128.0, 129.4, 130.2, 136.0, 138.0, 144.6, 145.5.

ESI MS: 262.2 (M+1).

9e: [7-Chloro-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]
acetonitrile.



Description : off-white solid.

HPLC Purity: 99.1%.

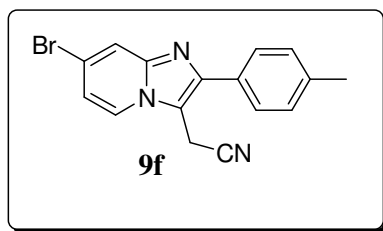
IR (IN KBr): 2246.9 cm¹.

¹H NMR (CDCl₃/TMS): δ 2.34 (s, 3H), 3.61 (s, 2H), 6.70 (dd, *J* = 1.7 Hz, *J* = 9.4 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 1.9 Hz, 1H), 8.48 (d, *J* = 9.4Hz, 1H).

¹³C NMR (CDCl₃/TMS): δ 15.5, 21.3, 116.4, 120.4, 124.0, 124.8, 125.7, 129.5, 130.0, 131.7, 134.8, 141.0, 145.5, 146.2.

ESI MS: 282.2(M+1);

9f: [7-Bromo-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]
acetonitrile.



Description : off-white solid.

HPLC Purity: 99.0%.

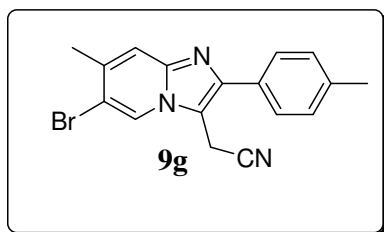
IR (IN KBr): 2248.8 cm¹.

¹H NMR (CDCl₃/TMS):δ 2.34 (s, 3H), 3.61 (s, 2H), 7.00 (dd, *J* = 1.7 Hz, *J* = 9.4 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 1.9 Hz, 1H), 8.57 (d, *J* = 9.4Hz,1H).

¹³C NMR (CDCl₃/TMS): δ 15.5, 21.3, 116.4, 125.7, 126.4, 127.0, 127.6, 129.5, 130.0, 131.7, 133.2, 134.8, 144.8, 145.5.

ESI MS: 326.2 (M+1), 328.2 (M+3).

9g: [6-Bromo-7-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl] acetonitrile.



Description : off-white solid.

HPLC Purity: 99.2%.

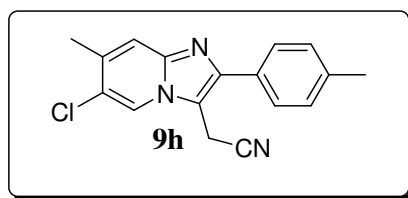
IR (IN KBr): 2243.8 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ 2.42 (s, 3H), 2.50 (s, 3H), 4.12 (s, 2H), 7.31 (d, $J = 7.7$ Hz, 2H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.57 (s, 1H), 8.22 (s, 1H);

^{13}C NMR (CDCl_3/TMS): δ 13.9, 21.2, 22.6, 106.8, 112.0, 114.8, 116.8, 122.8, 128.2, 129.6, 129.8, 136.0, 138.6, 144.6, 145.6.

ESI MS: 340.2 (M+1), 342.2 (M+3).

9h: [6-Chloro-7-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl] acetonitrile.



Description : off-white solid.

HPLC Purity: 99.2%.

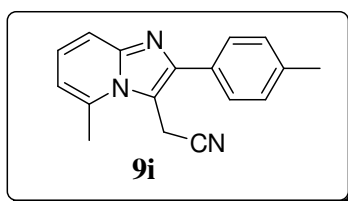
IR (IN KBr): 2247.3 cm^{-1} .

¹H NMR (CDCl₃/TMS): δ 2.34 (s, 3H), 2.36 (s, 3H), 3.61 (s, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.60 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 8.74 (s, 1H);

¹³C NMR (CDCl₃/TMS): δ 15.5, 19.9, 21.3, 116.4, 123.5, 125.1, 125.7, 129.5, 130.0, 131.7, 132.6, 134.8, 144.8, 145.5, 146.3.

ESI MS: 296.3(M+1).

9i: [5-Methyl-2-(4-methylphenyl) imidazo[1,2-a]pyridin-3-yl] acetonitrile.



Description : off-white solid.

HPLC Purity: 99.1%.

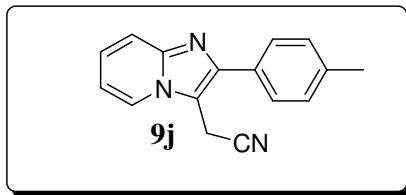
IR (IN KBr): 2242.2 cm⁻¹.

¹H NMR (CDCl₃/TMS): δ 2.41 (s, 3H), 2.45 (s, 3H), 4.12 (s, 2H), 6.81 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.44 (m, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.86 (m, 1H).

¹³C NMR (CDCl₃/TMS): δ 13.2, 21.7, 106.4, 115.5, 115.7, 116.2, 121.6, 128.2, 129.3 (2C), 130.4, 136.2, 138.2, 144.5, 145.8.

ESI MS: 262.2 (M+1).

9j: 2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-acetonitrile.



Description : off-white solid.

HPLC Purity: 99.3%.

IR (IN KBr): 2247.2 cm⁻¹.

ff-white solid; Yield 86%; purity by HPLC 99.3%; IR (cm⁻¹) 2247.2 (CN);

¹H NMR (CDCl₃/TMS): δ 2.43 (s, 3H), 4.16 (s, 2H), 7.00 (t, *J* = 6.4 Hz, 1H), 7.30 (d, *J* = 5.4 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 9.0 Hz, 1H), 8.05 (d, *J* = 6.8Hz, 1H).

¹³C NMR (CDCl₃/TMS): δ 13.8, 21.2, 107.3, 113.1, 115.0, 117.8, 122.7, 125.1, 128.2, 129.5, 130.1, 138.3, 145.1, 145.2.

ESI MS: 248.2 (M+1).

Preparation of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetic acid (10)

6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetonitrile was dissolved (16.5g, 63 mmol) in 50% sulfuric acid (100 mL) and the mixture was stirred under reflux at 110°C for a period of 4 - 5 hours. The reaction mixture was then cooled to 25-30°C, basified with 33% aqueous sodium hydroxide to pH 9.0, extracted with chloroform and the extract was discarded. The solution was given carbon treatment, stirred for 20 to 30.0min, filtered through a celite pad and acidified

to pH 5.5 using acetic acid. The white solid was filtered, washed with water and dried in the oven to obtain 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-acetic acid (**10**) as an off-white solid (15.9g, 90% yield and 99.9% purity by HPLC); IR (cm⁻¹) 1705 (COOH); ¹H NMR (DMSO+TFA, 400 MHz) δ 2.39 (s, 3H), 2.45 (s, 3H), 4.22 (s, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.56 (d *J* = 8.1 Hz, 2H), 7.88-7.90 (m, 2H), 8.81 (s, 1H), 11.67 (bs, 1H); ¹³C NMR (DMSO+TFA, 100 MHz) δ 17.5, 20.9, 29.1, 111.3, 116.7, 123.6, 124.8, 127.1, 128.2 (2C), 130.0 (2C), 133.2, 135.8, 137.9, 140.3, 169.8; ESI MS: 281.2 (M+1);

Preparation of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl)acetic acid (10) without isolation of intermediates starting from 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine (6)

100g (0.45 moles) of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine was dissolved (**6**) in 500 ml of acetic acid and the reaction mass was stirred. The reaction mass was cooled to 5-10 °C, 76g of 40% aqueous solution of dimethylamine slowly added followed by 17.7g of paraformaldehyde. The reaction mass was stirred at 50-55 °C for 3 hours and acetic acid was distilled under reduced pressure. 1000 ml of Water was added the solution was basified (pH 8.0) by adding 30% sodium hydroxide solution. The solution was extracted with 3x300 ml of dichloromethane, the organic layer was washed with water (500 ml) and brine solution (500 ml). It was then dried with anhydrous sodium sulfate, filtered and distilled the solvent until the

volume reached to around 300 ml. This solution containing 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-N,N-dimethylmethylamine (**7**), 89% purity by HPLC, and it was used further as such.

The above organic solution was cooled to 0 to 5 °C, ethylchloroformate was added (58.3g, 0.54 moles) slowly over a period of 30 minutes. The reaction mass was stirred for one hour at the same temperature, the solvent distilled off under reduced pressure to obtain carbamate salt as bright yellow colored solid. This solid was dissolved in 300 ml of water, and basified the solution to pH 7.5-8.0 using 10% sodium hydroxide solution. Then sodium cyanide (26.5g, 0.54 moles) was added and the reaction mass was stirred at 50-55 °C for 3 hours. The reaction mass was then cooled to room temperature and the yellow solid was filtered and washed with 500 ml of water. This crude solid contained 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-acetonitrile (**9**), 82% purity by HPLC, and was used for hydrolysis without any further purification.

The above crude solid was dissolved in 624 ml of 50% sulfuric acid, and stirred at 110 °C for 4 hours. Then the reaction mass was cooled to room temperature and 2.5 liters of ice cold water was added to the mass. The solution was basified to pH 9.0 extracted with MDC (2x300.0ml), aqueous layer was separated, treated with carbon, stirred for about 30.0min, filtered through a pad of celite and the filtrate was acidified to pH 5.5 using acetic acid. A white solid precipitated, which was filtered washed with water and dried in air

flow oven at 60-65°C until it constant weight. 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetic acid (**10**) was obtained as an off-white solid (78.0g, 99.5% pure by HPLC. 61.9% overall yield). Melting point: 234.0-235.2 °C; IR spectra (cm⁻¹): 3427, 2919, 1701, 1508, 1183, 827, 805; Mass (m/z): 281.2 (M+H)⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.31 (s, 3H), 2.34 (s, 3H), 4.08 (s, 2H), 7.17 (dd, *J* = 9.1 Hz, *J* = 1.5 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 9.1 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 8.22 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 17.57, 20.93, 29.16, 111.36, 116.75, 123.69, 124.88, 127.11(2C), 128.23(2C), 130.08, 133.22, 135.82, 137.93, 140.33 and 169.83.

Preparation of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-N,N-dimethylacetamide (1).

To the suspension of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetic acid (**10**) (20g, 71.4mmol) in dichloromethane (500mL) was added triethylamine (10g, 99 mmol) maintaining the temperature at 0 - 5°C. Then pivaloyl chloride (11.2g, 93.3mmol) was added to the above reaction mass and stirred for 30 minutes. After completion, 40% aqueous solution of dimethylamine (18 mL, 160mmol) was added in one lot at 0 - 5°C and the reaction mass stirred for 30 minutes. Later 5% aqueous sodium hydroxide solution (150 mL) was added and the reaction mass stirred for 10 minutes, the organic layer was separated, washed with water (100mL), brine solution (100mL), dried with anhydrous sodium sulfate and filtered. The solvent was distilled under reduced pressure, n-hexane (100mL)

was added to the residue and stirred for a period of 15 minutes. The solid was filtered and washed with n-hexane (20 mL), and dried in the oven to obtain 6-methyl-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-N,N-dimethylacetamide (**1**) as white solid (20.8g, 90% yield and 99.8% purity); IR (cm⁻¹) 1635 (C=O); ¹H NMR (CDCl₃, 400 MHz) δ 2.34 (s, 3H), 2.40 (s, 3H), 2.88 (s, 3H), 2.94 (s, 3H), 4.09 (s, 2H), 7.04 (dd, *J* = 9.15 Hz, *J* = 1.58 Hz, 1H), 7.26 (d, *J* = 7.87 Hz, 2H), 7.55-7.52 (m, 3H), 8.00 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 168.03, 142.79, 142.40, 136.48, 131.93, 129.12, 127.58, 127.04, 122.35, 120.64, 115.79, 115.22, 36.94, 35.29, 28.88, 20.79, 17.76; ESI MS: 308.5 (M+1);

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