CHAPTER – V

SYNTHESIS OF 3-METHYLSULFANYL-2-(p-TOLYL) IMIDAZO[1,2-a] PYRIDINE DERIVATIVES

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5.1 INTRODUCTION:-

Imidazo[1,2-a]pyridine derivatives are one important class of alkaloids frequently found in natural products.[1,2] Their biological activities caused them being often used as building blocks in the synthesis of important drugs and therapeutically active molecules.[3-6] Functionalized imidazo[1,2-a]pyridines and other imidazo fused heterocycles are prevalent structural motifs in pharmaceutically important compounds.[7-10] Functionalization at 2 and 3 position of imidazo[1,2-a]pyridines have great impact, as substituents at these positions display biological activity.[11] Since the discovery of the potential utility of 3-sulfenyl derivative of indoles as pharmaceuticals,[12] significant efforts have devoted to the development of new sulfenyl substituted indoles and related compounds.[13-15] In contrast to the ever growing literature on sulfenyl substituted indoles, examples of imidazopyridines incorporating these functionalities remain very scarce.[16]

The methylsulfanyl (thiomethyl) functionality has found wide application in biologically active molecules.[17-20] Further these substituted heterocycles have also found application in metal catalyzed cross-coupling reactions.[21-23] There exists a limited number of methods exist for introduction of thiomethylether in heterocyclic systems.

Recently copper mediated thiomethylation of aryl and heteroaryl system using dimethylsulfoxide as the source of thiomethyl group.[24-26] These reactions employ metal catalysts and require higher temperatures. Thiomethylation of imidazo[1,2-a]pyridines has not been fully explored. This prompted us to explore the use of activated DMSO to develop a novel approach for thiomethylation of these compounds. In this chapter, we present a new approach for the synthesis of 3-methylsulfanyl imidazo[1,2-a]pyridines (**Fig: a**)using DMSO and alkyl bromide.

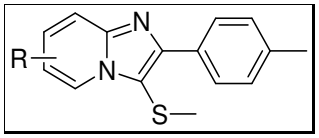
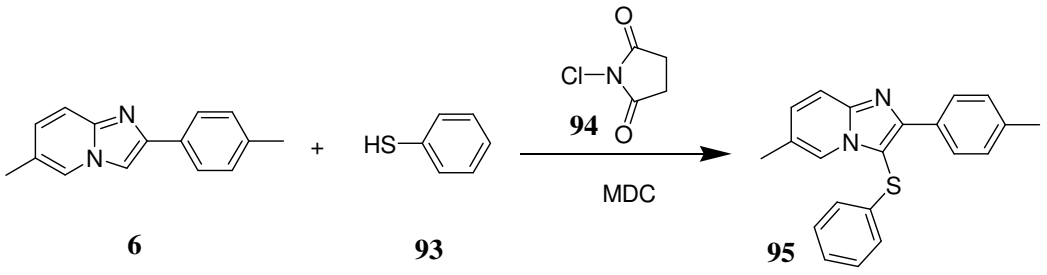


Fig: a

5.1 LITERATURE BACKGROUND

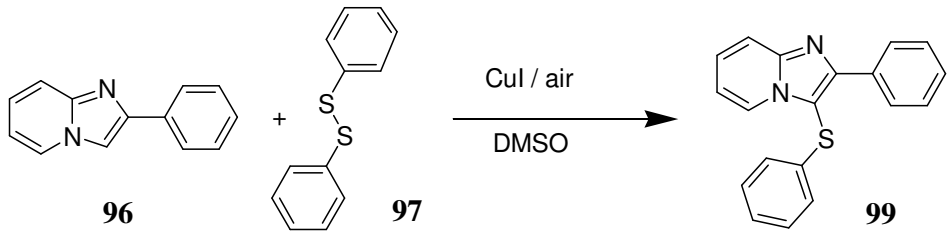
Chitrakar[27] et al reported the synthesis of 6-methyl 3-(thiophenyl)-2-(p-tolyl)imidazo[1,2-a]pyridine **95** by the reaction of 6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridine **6** with thiophenol **93** in dichloromethane solvent in the presence of N-chloropyrrolidine-2,5 -dione **94** to produce **95** (**Scheme-5.1).**



6 **93** **95**

(Scheme-5.1)

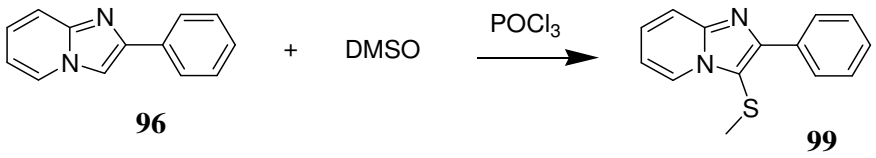
Zhou[28] et al reported the synthesis of 2-phenyl-3-(thiophenyl) imidazo[1,2-a]pyridine **98** by the reaction of 2-Phenylimidazo[1,2-a] pyridine **96** with 1,2-diphenyldisulfane **97** in DMSO containing cuprousiodide as catalyst to produce **98 (Scheme-5.2).**



96 **97** **99**

(**Scheme-5.2)**

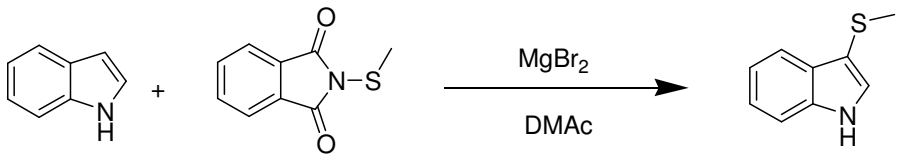
Abhijit[29] et al reported the synthesis of 2-Phenyl-3(thiomethyl) imidazo[1,2-a]pyridine **99** by the reaction of 2-Phenylimidazo [1,2-a]pyridine **96** with $POCl_3$ in DMSO to produce **99 (Scheme-5.3)**



96 **99**

(Scheme-5.3)

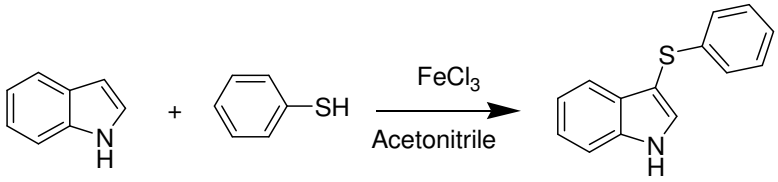
Matthew[30] et al reported the synthesis of 3-(thiomethyl)-1*H*-indole **101** by the reaction of Indole **58** with N-thioarylphthalimide **100** in Dimethylacetamide (DMAc) containing magnesium bromide produce **101 (Scheme-5.4).**



58 **100** **101**

(Scheme-5.4)

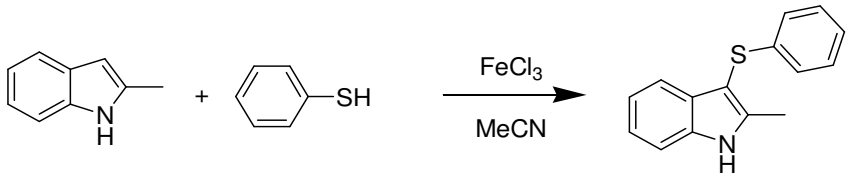
Subbareddy[31] et al reported the synthesis of 3-(thiophenyl)-1*H*-indole **102** by the reaction of indole **58** with thiophenol **93** in acetonitrile containing $FeCl_3$ to produce 3-thiophenyl indole **102 (Scheme-5.5).**



58 **93** **102**

(**Scheme-5.5)**

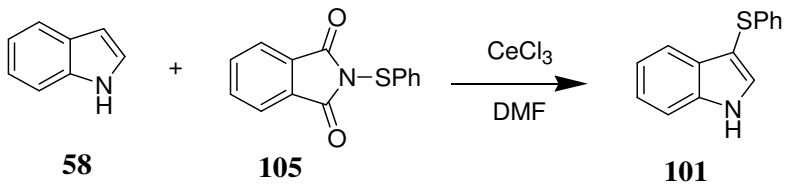
Fang[32,33] et al reported the synthesis of 2-methyl-3-(thiophenyl)-1*H*-indole **104** by the reaction of 2-methyl-1*H*-indole **103** with thiophenol **93** in presence of iron (III) chloide in acetonitrile to produce 2-methyl-3-thiophenyl indole **104 (Scheme-5.6).**



103 **93** **104**

(**Scheme-5.6)**

Claudio[34] et al reported the synthesis of 3-(Phenylthio)-1*H*-indole **101** by the reaction of indole **58** with N-thiophenylpthalimide **105** in DMF containing cerium (III) chloride **104** to produce **101 (Scheme-5.7).**



58 **105** **101**

(**Scheme-5.7)**

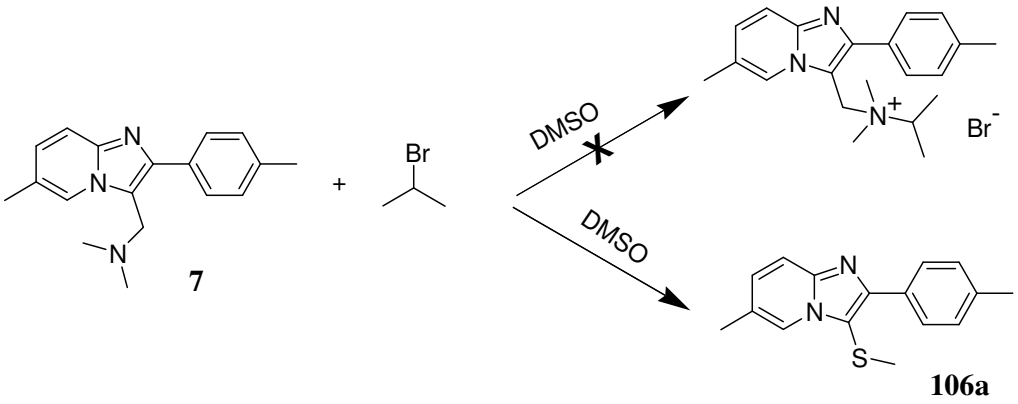
5.3 PRESENT WORK:

We have developed a new synthetic route for the synthesis of 3-thiomethylimidazo[1,2-a]pyridines. The synthesis involves use of isopropylbromide and dimethyl sulfoxide (DMSO). It is obvious from the reference cited above that only limited numbers of methods are reported for introduction of a thiomethy group in heterocyclic systems. We report a practical and metal free method for the synthesis of 3-thiomethyl imidazo[1,2-a]pyridine using DMSO activated by isopropyl bromide.

5.4 RESULTS AND DISCUSSION

In our research work, we focused for the synthesis of a quaternary salt[35] of mannich base, 3-(N,N- dimethylaminomethyl)-2-(*p*-tolyl)-6-methyl imidazo [1,2-a]pyridne, by avoiding volatile methyliodide and to develop a simplified process for the synthesis of hypnotic drug zolpidem. Initially, we tried to use alkylbromides for the substitution of methyliodide. For this, Dimethylaminomethyl derivative **7** treated with isopropylbromide instead of methyliodide in the presence of

dimethylsulfoxide with expectations of a quaternary salt. Surprisingly, we found the obtained product in this reaction is 6-methyl-3-(thiomethyl)-2-(p-tolyl)imidazo[1,2-a]pyridine (**106a) Scheme-5.8.**

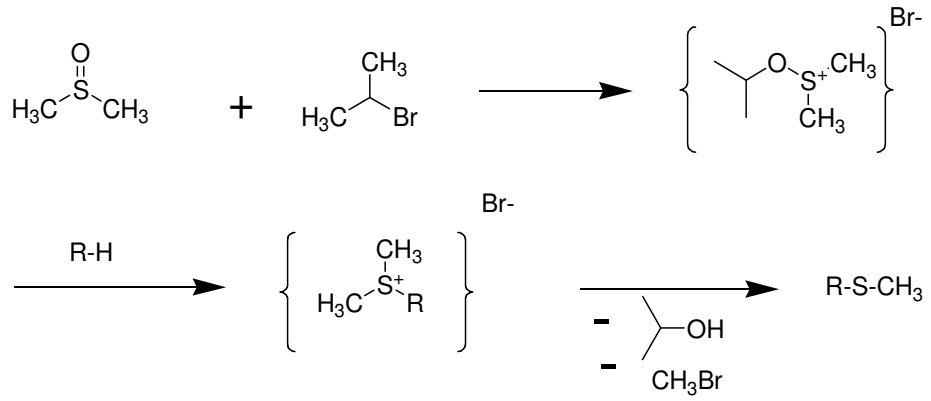


(Scheme-5.8)

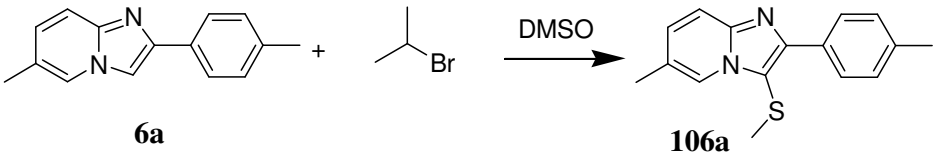
This result heaved our interest and found in the literature that DMSO can be used as the source of thiomethyl group, but simple alky bromides as activators did not identified. Thus, 6-methyl-2-(p-tolyl) imidazo[1,2-a]pyridine (**6a)** treated with isopropylbromide in presence of dimethylsulfoxide at 70-75^{0}C (**scheme 5.10).** In similar fashion, as observed in the case of mannich base derivative, formed 6-methyl-2-(p-tolyl)-3-thiomethylimidazo[1,2-a]pyridine **106a**. When this reaction repeated with other simple alkyl bromides, such as benzylbromide, n-propylbromide and 1,2-dibromoethane the same product formed.

In order to understand the plausible mechanism of this reaction, reaction monitored by GC-MS. We found isopropylbromide, isopropyl alcohol and methylbromide were the byproducts of this reaction. Based on these results we assumed the following mechanism for this reaction

and represented in (**Scheme-5.9)**. We prepared a series of 3-substituted thiomethyl derivatives of imidazo[1,2-a]pyridines to ascertain the process and presented in **Table 5.1**.

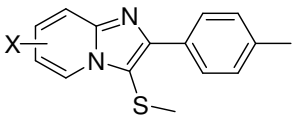


(Scheme 5.9)



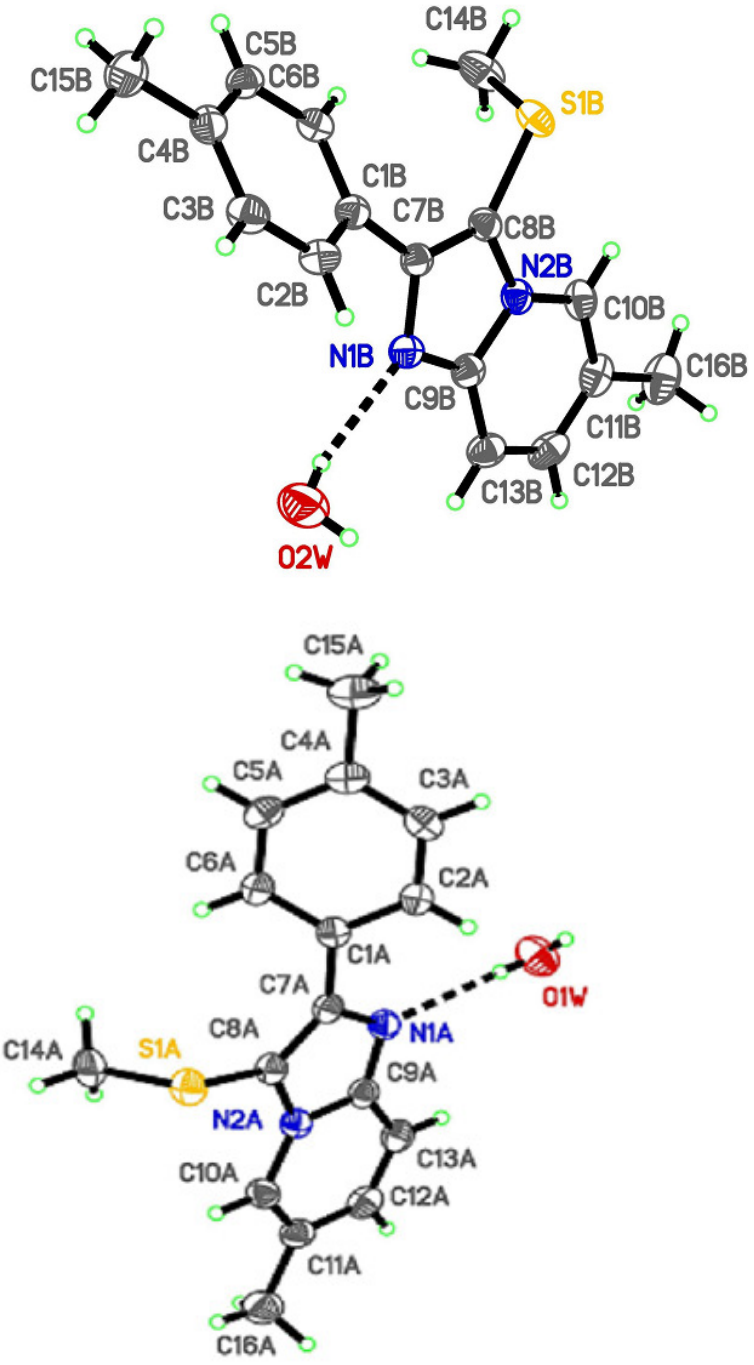
(Scheme 5.10)

Table 5.1: Various substituted 3-thiomethyl derivatives of imidazo[1,2-a]pyridines.

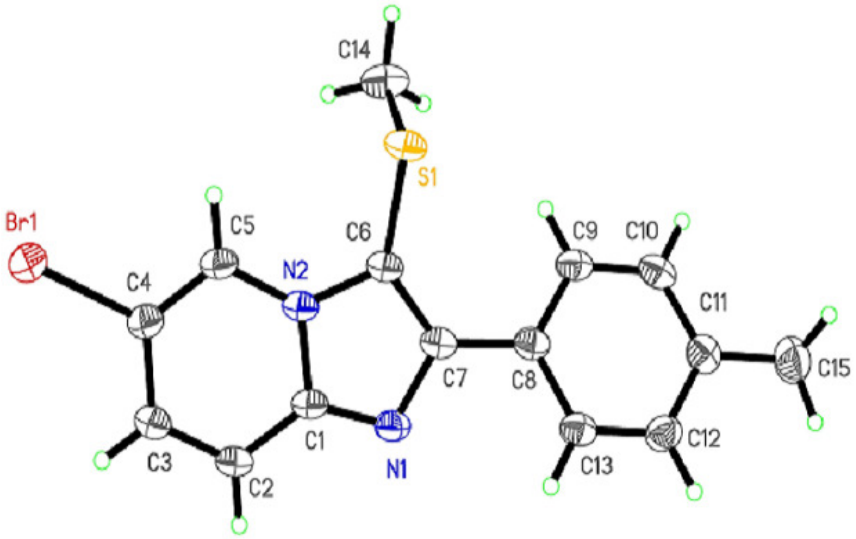


Entry	Product	X	Time	Yield
1	106a	6- Methyl	18.0h	78%
2	106b	6-Bromo	18.0h	75%
3	106c	7-Methyl	18.0h	82%
4	106d	6-Chloro	18.0h	64%
5	106e	H	18.0h	62%

All the synthesized compounds were analyzed by their spectral data and confirmed their structures. The typical structure of 6-methyl-2-(p-tolyl)-3-thiomethylimidazo [1,2-a]pyridine (**106a)** was discussed based on spectral data. Its **^{1}H NMR** ($CDCl_3$/TMS) spectrum **(Fig-5.1)** showed signals as δ 2.24 (s, 3H), 2.38 (s, 3H), 2.40 (s, 3H S-C**H$_3$**), 7.12 (d, *J* = 8.8 Hz, 1H aromatic **-CH**), 7.29 (d, *J* = 7.9 Hz, 2H aromatic **-CH**), 7.55 (d, *J* = 9.0 Hz, 1H aromatic **-CH**), 8.19 (d, *J* = 8.0 Hz, 2H aromatic **-CH**), 8.24 (s, 1H aromatic **-CH**). Its **^{13}C NMR** ($CDCl_3$/TMS) spectrum **(Fig-5.2)** showed signals at δ 18.05, 18.29, 21.21, 110.38, 116.75, 121.88, 122.18, 127.90, 128.70, 128.93, 131.06, 137.79, 145.22, 148.65; Peak at 2.40ppm in PMR and 18.3ppm in CMR corresponds to thiomethyl group. **ESI** mass spectrum **(Fig-5.3)** showed molecular ion peak at 269.0 (M+1) related to molar of **106a**. Sulphur atom presence confirmed by its elemental analysis. The assigned structures for **106a**, **106b** and **106c** further established by their single crystal X-Ray analysis and presented below.

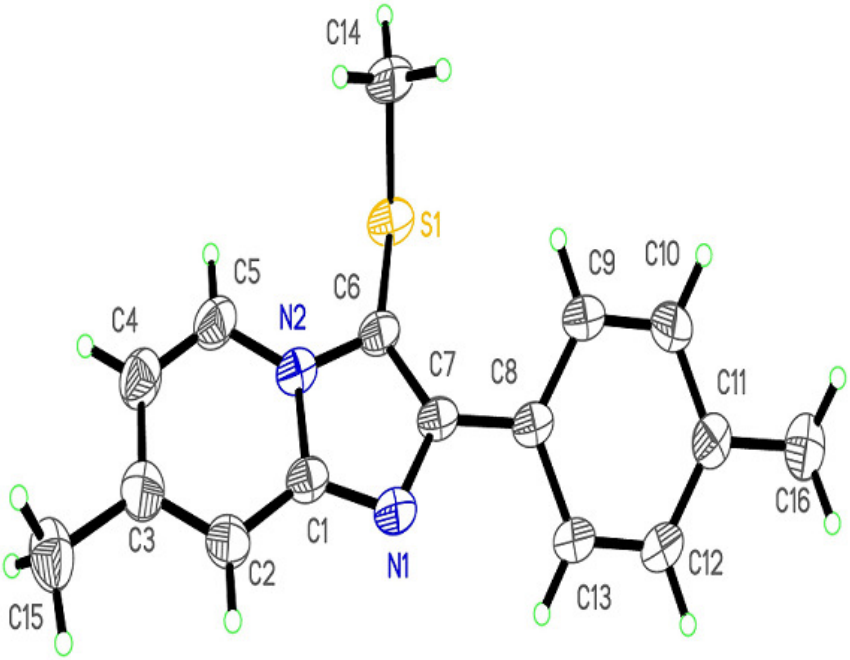


Front and Rare view of X-Ray crystal structure for 6-Methyl-3-(thiomethyl)-2-(p-tolyl)imidazo[1,2-a]pyridine (106a).



X-Ray crystal structure for

6-Bromo-3-(thiomethyl)-2-(p-tolyl)imidazo[1,2-a]pyridine (106b)



X-Ray crystal structure for

7-Methyl-3-(thiomethyl)-2-(p-tolyl)imidazo[1,2-a]pyridine (106c)

CONCLUSION:

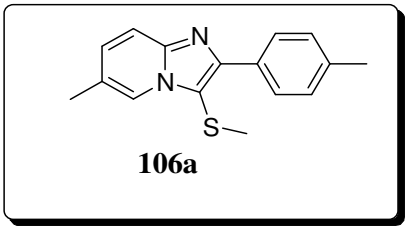
In summary, We have developed a simple method for thiomethylation of imidazo[1,2-a]pyridines using DMSO and isopropylbromide as a reagent. The reaction conditions are uncomplicated and obtained moderate to excellent yields.

5.5 EXPERIMENTAL SECTION:

General Procedure:-

A mixture of imidazo[1,2-a]pyridine (9.1mmol) and isopropyl bromide (18.2mmol) in DMSO 20ml was heated at 70-75^{0}C for 18h. After completion of the reaction, reaction mass was cooled to room temperature, diluted with water and extracted with dichloromethane (20ml X 2). The organic extracts were combined and washed with water (20ml), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography by using 5-10% ethylacetate in n-hexane as eleunt.

106a: 6-Methyl-3-(thiomethyl)-2-(p-tolyl)imidazo[1,2-a]pyridine.



106a

Description : White solid.

Melting point : 131.7 – 133.4^{0}C.

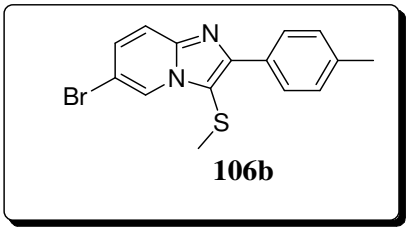
IR (IN KBr) : 3419, 2918, 1502, 1468, 1433, 1409, 1316, 1245, 1148, 1165, 1148, 1021, 971, 828, 799, 727, 571, 517cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ 2.24 (s, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 7.01 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 8.24 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS): δ 18.05, 18.29, 21.21, 110.38, 116.75, 121.88, 122.18, 127.90, 128.70, 128.93, 131.06, 137.79, 145.22, 148.65.

ESI-MS:(m/z): 269.0(M+1).

106b: 6-Bromo-3-(thiomethyl)-2-(p-tolyl)imidazo[1,2-a]pyridine.



106b

Description : White solid.

Melting point : 152.3–156.7^{0}C.

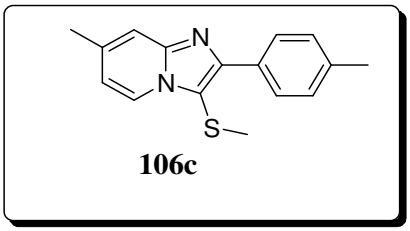
IR (IN KBr) : 3410, 3046, 3013, 2919, 1510, 1494, 1470, 1409, 1331, 1312, 1064, 839, 829, 816, 727, 517cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ 2.27 (s, 3H), 2.42 (s, 3H), 7.35 (m, 3H), 7.55 (d, *J* = 9.4 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 8.60 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS): δ 18.07, 21.23, 107.41, 118.03, 124.35, 127.92, 129.07, 129.09, 130.39, 138.36, 144.57, 149.45.

ESI-MS:(m/z:) 335.1 (M+1).

106c: 7-Methyl-3-(thiomethyl)-2-(p-tolyl)imidazo[1,2-a]pyridine.



106c

Description : White solid.

Melting point : 132.2 -133.8°C.

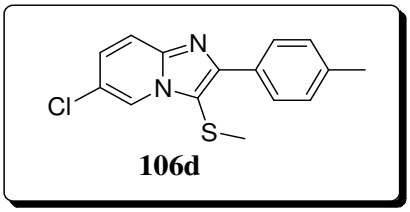
IR (IN KBr) : 3401, 2917, 1641, 1492, 1476, 1437, 1409, 1334, 1351, 1233, 1185, 1166, 1036, 1013, 971, 853, 828, 793, 773, 727,, 511cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ 2.24 (s, 3H), 2.41 (s, 3H), 2.44 (s, 3H), 6.76 (d, *J* = 6.7 Hz, 1H), 7.27 (d, *J* = 4.4 Hz, 2H), 7.41 (s, 1H), 8.18 (d, *J* = 7.9 Hz, 2H), 8.35 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS): δ 18.14, 21.21, 110.07, 115.03, 115.94, 123.25, 127.92, 128.93, 131.04, 136.73, 137.82, 146.59, 148.70.

ESI-MS:(m/z): 269.1(M+1).

106d: 6-Chloro-3-(thiomethyl)-2-(p-tolyl)imidazo[1,2-a]pyridine.



106d

Description : White solid.

Melting point : 150.8 -154.3^{0}C.

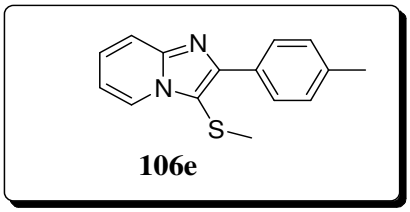
IR (IN KBr) : 3428, 3048, 3019, 2921, 1515, 1494, 1473, 1465, 1413, 1331, 1312, 1221, 1076, 830, 818, 730, 703, 517cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ 2.24 (s, 3H), 2.40 (s, 3H), 7.28 (m, 3H), 7.58 (d, *J* = 9.4 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 2H), 8.48 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS): δ 18.01, 21.21, 111.68, 117.78, 120.95, 122.09, 126.94, 127.59, 127.90, 129.05, 129.11, 130.48, 138.31, 144.49, 149.70.

ESI-MS:(m/z): 289.1(M+1).

106e: 3-(Thiomethyl)-2-(p-tolyl)imidazo[1,2-a]pyridine.



106e

Description : White solid.

Melting point : 106.2- 109.5^{0}C.

IR (IN KBr) : 3032, 1631, 1496, 1473, 1344, 1314, 1230, 1178, 1146, 963, 849, 831, 755, 743, 726, 516 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ 2.24 (S, 3H), 2.39 (S, 3H), 6.94 (t, *J* = 6.6 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 3H), 7.67 (d, *J* = 8.9 Hz, 1H), 8.17 (d, *J* = 7.9Hz, 2H), 8.47 (d, *J* = 6.6Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS): δ 18.01, 21.24, 110.95, 112.59, 117.35, 124.09, 125.84, 128.02, 128.97, 128.99, 129.1, 130.66, 138.09, 146.07, 148.68.

ESI-MS:((m/z): 255.1(M+1).

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