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Green chemical route for process development of lansoprazole intermediate

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ABSTRACT

One of the most important researches in chemistry is to substitute hazardous reactions into safe Green Chemistry reactions. Green chemistry is based on a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products.[9][10][11]

Keywords: Green Chemistry, Reaction, Appel reaction

INTRODUCTION

Lansoprazole is a proton pump inhibitor, largely used in the treatment of peptic ulcers. Manufacturing process of Lansoprazole is of seven stages, the most important and critical stage is to convert Lanso- Alcohol to Lanso- Chloro which is generally done with thionyl chloride. This stage is very much time consuming as it is a controlled temperature reaction. Also gases like HCl and SO_2 are generated as by products of this reaction. Keeping in mind the need for avoiding hazardous chemicals which harm our environment and human beings, current process is developed using application of Appel's reaction.[7][8][9]

MATERIALS AND METHODS

Purity of the compound was monitored on silica gel 60 F_{254} purchased from Merck and solvent from Aldrich chemical Co Ltd. Anhydrous silica gel 60 was used as solid support after dehydration in oven at 100°C for 5 minutes. Mobile phase used was Benzene: Chloroform: Methanol (5:3:2) as an eluent. TLC spots were detected in UV chamber. Melting point of synthesised compound was determined on open capillary in liquid paraffin. Structural interpretation was done by performing Mass spectra, IR and HPLC which were compared with reference standard.

Green Chemical route for synthesis of 2-chloro methyl-3-methyl-4-(2, 2, 2-trifluoro ethoxy) pyridine hydrochloride (Lanso Chloro)

2 mole of PPh_3 was dissolved in 5 mole of carbon tetrachloride at 10- 15°C and 1 mole of Lanso Alcohol was added to above solution under stirring. 10 mole of MDC was added as a solvent , reaction mass was stirred for 10 min and then added 0.2 mole of tetra methyl ammonium bromide and 1.0 mole tri ethyl amine at 15 -20°C. [9]Reaction mass was stirred for 15 min, the temperature raised to RT and then slowly heated to 40 -45° C for 4-5 hr. Reaction was monitored till completion on TLC. Reaction mass was chilled to 0-5°C and maintained for 2 hr. Reaction mass was filtered, solid obtained was washed with chilled acetone and then with toluene. Solid was dried at 55-60°C to get Lanso Chloro. Purity of the compound was matched with standard Lanso Chloro and found to be 99.98% on HPLC [3][4]

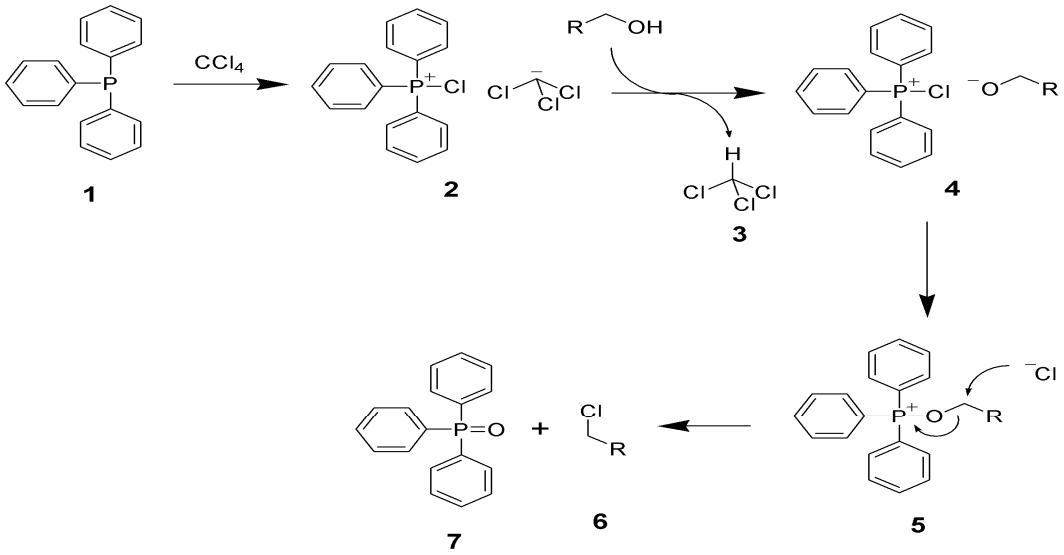
Properties:

Description: White to off –white crystalline powder
Solubility: Freely soluble in water, soluble in methanol, insoluble in Ether
Melting Range: Between 205°C to 210°C

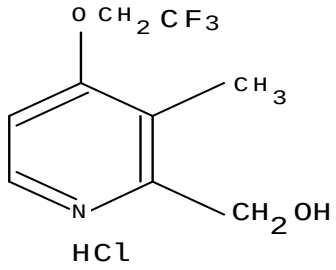
Purity by HPLC: 99.98 %

Reaction Mechanism:

The reaction proceeds by activation of the triphenylphosphine [**1]** by reaction with the tetrahalomethane, followed by attack of the alcohol oxygen at phosphorus [**4]** to generate an oxyphosphonium intermediate [**5**]. The oxygen is then transformed into a leaving group, and an S_N2 displacement by halide takes place, proceeding with inversion of configuration if the carbon is asymmetric[5].[6]

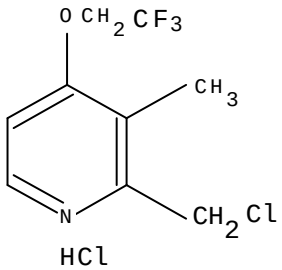


Reaction of Lanso chloro



2-(hydroxymethyl)-3-methyl-4-(2,2,2-trifluoroethoxy) pyridine hydrochloride

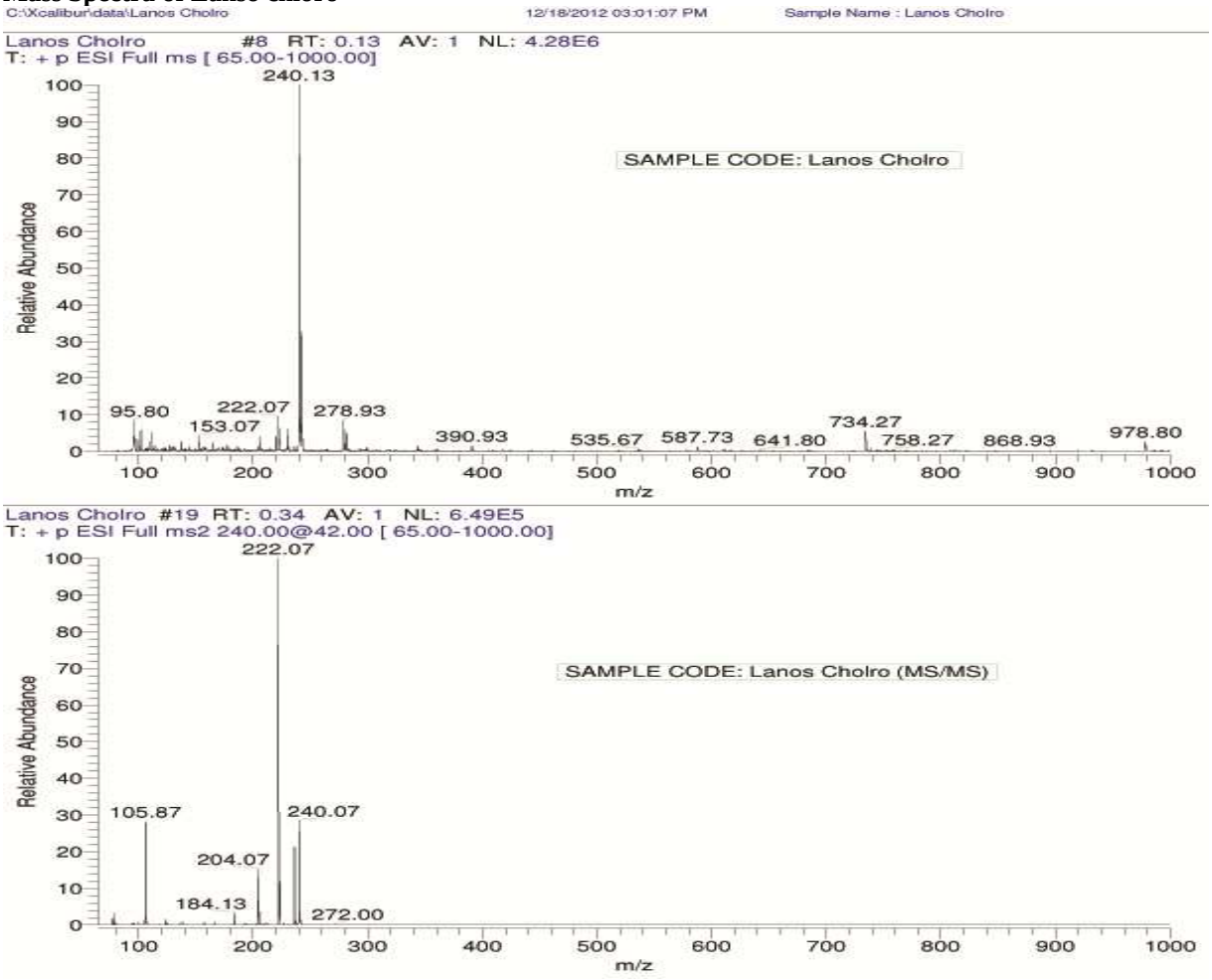
CCl_4
MDC
Tri ethyl amine
Tetra methyl ammonium Bromide



2-(Chloromethyl)-3-methyl-4-(2,2,2-trifluoroethoxy) pyridine hydrochloride

Synthesized Lanso Chloro intermediate of Lansoprazole was matched with standard Lanso Chloro intermediate by HPLC and by Mass Spectra.[1][2]

Mass Spectra of Lanso chloro



IR Spectra

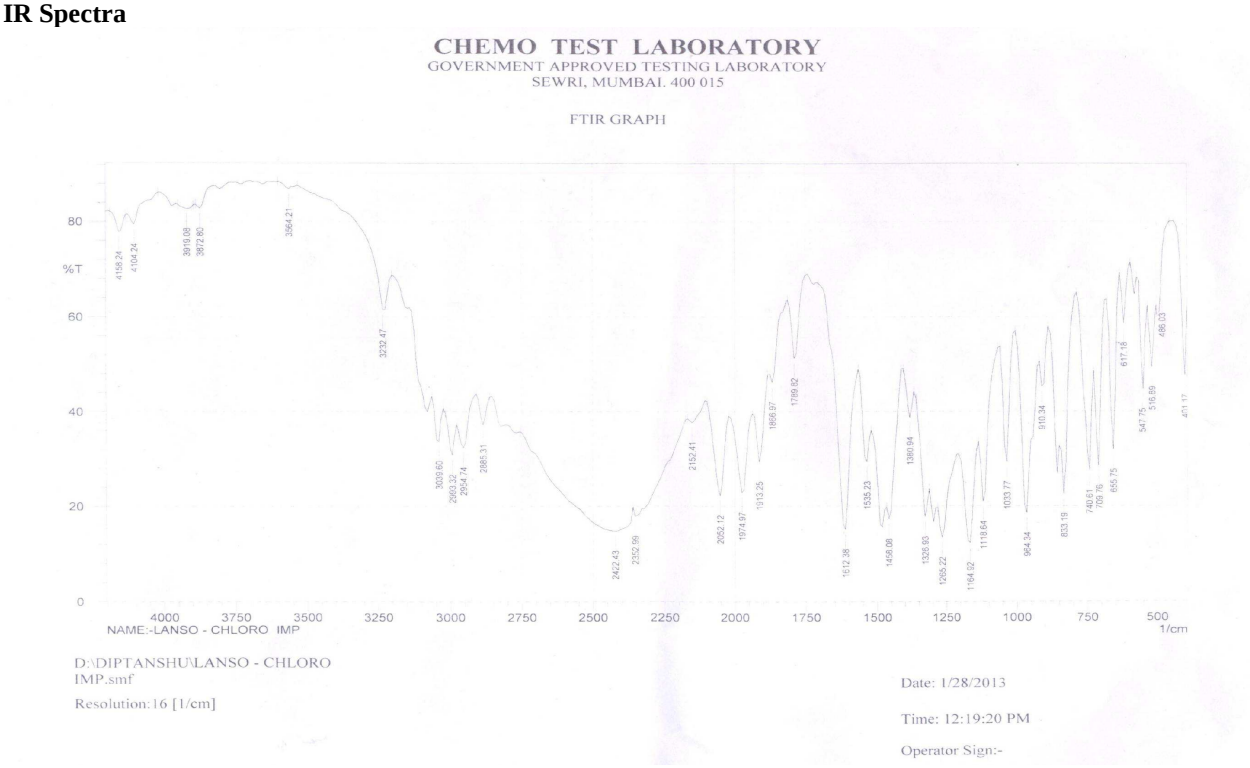


Fig 1:Blank

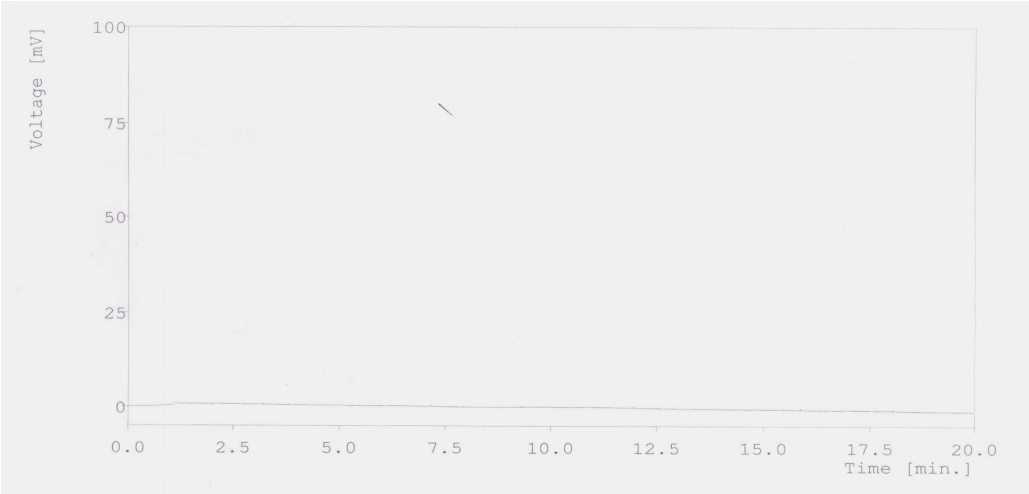


Fig 2: WS Lanos chloro intermediate

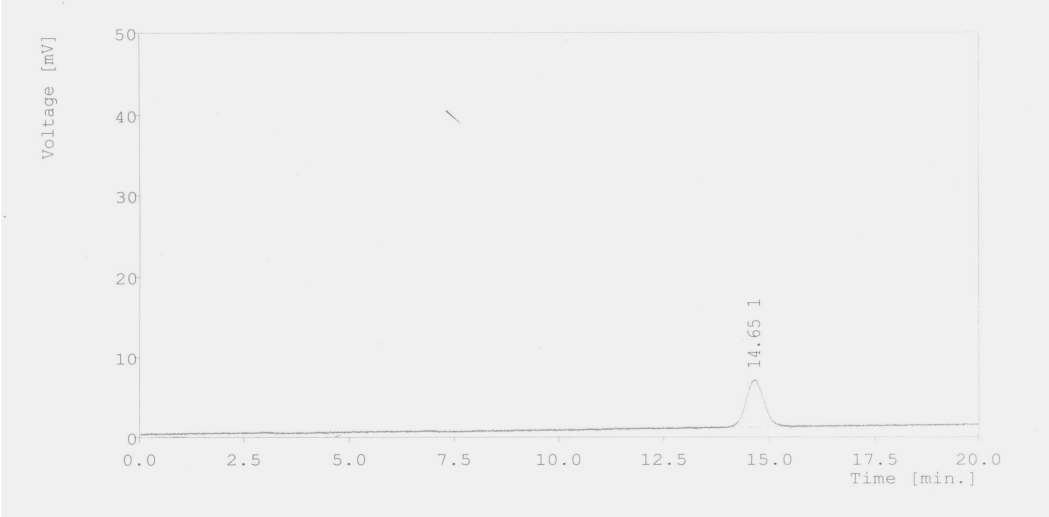
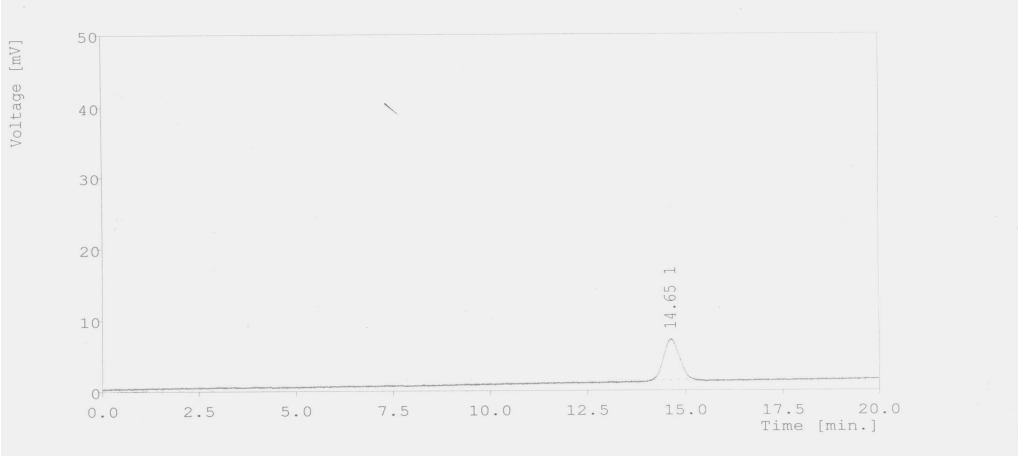


Fig 3: Sample of Lanso chloro intermediate



CONCLUSION

Generally Chlorination reaction is carried out by thionyl chloride which leads to the formation and release of hazardous gases like SO_2 and HCl. However by synthesizing Lansoprazole Chloro intermediate using Appel's

reaction, the Green chemistry route is achieved by eliminating release of hazardous gases and also minimizing the time required for completion of reaction. Purity of this compound is 99.98% of Standard.

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