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ALTERNATIVE, COST EFFECTIVE SYNTHESIS OF (3-(2-(DIMETHYLAMINO) ETHYL)-1H-INDOL-5-YL) METHANOL FROM 5-BROMO-1H-INDOLE

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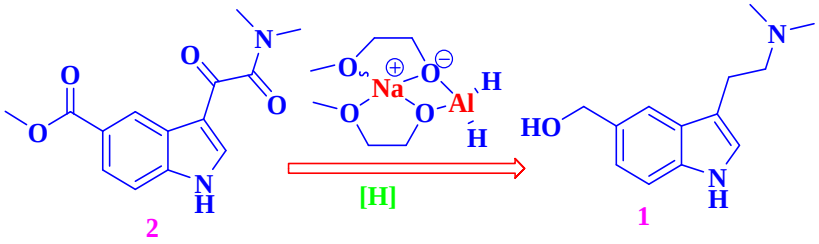
ABSTRACT

Synthesis, characterization of a key starting material (3-(2-(dimethylamino) ethyl)-1H-indol-5-yl) methanol from commercially available raw material 5-Bromo-1H-indole; the main improvement in this synthesis is the simultaneous reduction of three carbonyl groups at time with an inexpensive reagent vitride.



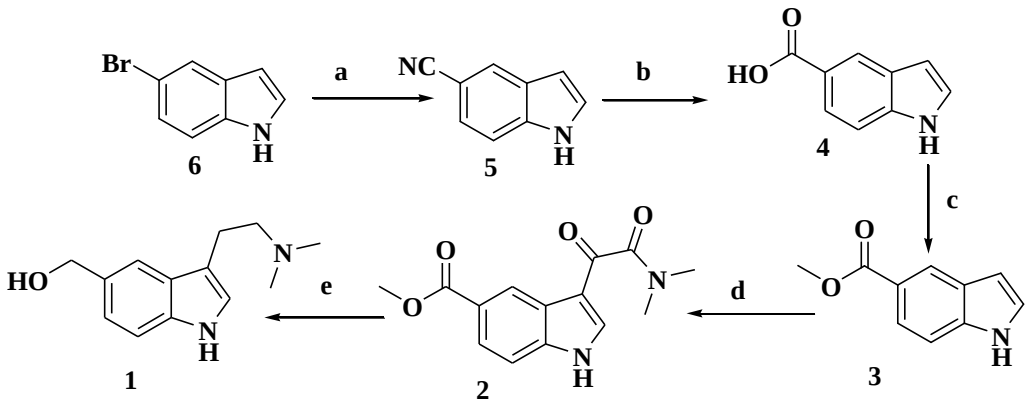
KEYWORDS: Synthesis, Indole derivative, vitride, selective reduction of three carbonyl groups with less pyrophoric reducing agent

INTRODUCTION

Anti-migraine drug substances like Almotriptan, sumatriptan, rizatriptan, Avitriptan were having common featured functionalized 3, 5-substituted 1H Indole. These triptan derivatives were constructed with different heterocyclic building blocks which are interconnected with Indole. J. Alvarez-Bulla etal, was reported[1] the process for the preparation of (3-(2-(dimethylamino) ethyl)-1H-indol-5-yl) methanol as a part of synthesis of sumatriptan C-dimer impurity from starting from methyl1H-indole-5-carboxylate, which was acylated with Oxalyl chloride at 3-position, amidation with dimethyl amine and followed by carbonyl

reduction with Lithium Aluminium hydride (LAH). As we know that LAH is more expensive and pyrophoric in nature. Dueto its pyrophoric nature it is very difficult to use in commercial level, handling is so critical and not cost effective also in bulk scale manufacturing. Therefore, in the present innovation the author's explored simultaneous reduction of three carbonyl groups such as Amide, Keto, and Ester with commercially available less pyrophoric and cost effective reagent Vitride[2,3] or Red-Al or synhydrid, chemically known as sodium bis (2-methoxyethoxy) aluminium hydride which safer alternative to Lithium Aluminium hydride[4] and other hydride agents. The most advantage of Vitride is it can tolerates the temperatures up to 200 °C, under dry conditions, It has unlimited shelf life. It is soluble in aromatic solvents, whereas LAH is only soluble in ethers.

Scheme-I



a: Cu(I)CN, DMF, 130^{0}c, 4 hours; b: 25% NaOH, HCl; c: CH_3I, K_2CO_3, DMF; d: $(COCl)_2$,DMA; e: Vitride

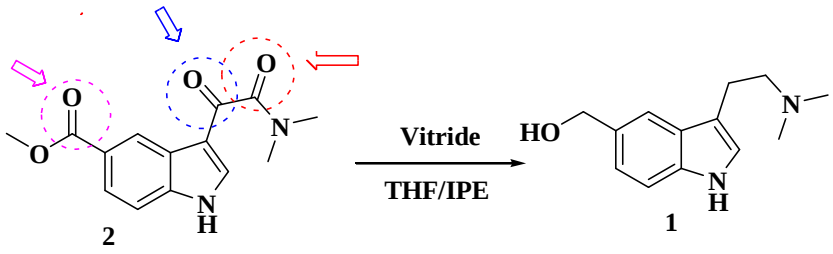
RESULTS AND DISCUSSION

The synthesis of compound 1 is initiated with commercially available 5-bromo-1H-indole (6), In the first stage of the synthesis compound 5 was treated with copper(I) cyanide in Dimethyl formamide solvent to obtain compound 5 with 80% yield. The Nitrile group present in compound 5 was taken for base hydrolysis to obtain compound 4 (the nitrile converted carboxylic acid) which was subjected for esterification with methyl iodide in DMF, potassium carbonate and the triggered compound 3 in esterification was taken for friedal craft acylation followed by amidation at third position of Indole moiety of compound 3 with Oxalyl chloride and N, N-Dimethyl amine (DMA) to get compound 2.

The present invention / improvement in the process from compound 2 to compound 1. The three carbonyl groups present in Compound 2 methyl ester carbonyl at 5th position of Indole

moiety (as shown as in scheme II) and the other two carbonyls present at 3rd position in the same moiety (Keto and Amide carbonyls) were previously reported in Lithium Aluminium hydride, which is more expensive, pyrophoric in nature and hence this reducing gent is not preferable commercial industrial applications.

Scheme-II



It is achieved the three different environmental, natured carbonyl groups reduction simultaneously with simple and commercially available, less expensive reducing agent Vitride or Red-Al (Scheme-II). Being compound 1 is having more industrial applications, It must be synthesized in commercially viable synthetic routes and it should be define operationally safety process. Therefore the authors attempted a successful pathway with alternative reagent methodology to produce the compound1 known as (3-(2-(dimethylamino) ethyl)-1H-indol-5-yl) methanol.

EXPERIMENTAL SECTION

All the raw materials used for its selected route of synthesis (Scheme I) is procured from commercial manufacturing source and the Reagents grade materials were purchased from AVRA synthesis. All the solvents used for its entire process were procured from commercial solvents supplié Merck Inc., and Chem pure. The melting points were measured in capillary tubes and are uncorrected. FT-IR spectra were determined by Perkin Elmer Spectrum 100 by using 1% potassium bromide pellet technique. 1H, 13C NMR spectra were obtained at 400 MHz, Chemical shifts (δ) were determined using TMS as internal standard, and multiplicity (s, singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet; m, multiplet). HPLC-MS analyses were performed on Shimadzu 2020 apparatus. All yields correspond to isolated pure compounds. 5-bromo-1H-Indole has been obtained from commercial source.

The synthesized compounds were confirmed by spectral identification by 1H & 13 NMR (Bruker 400M Hz), and Mass (SHIMADZU-MS), FT-IR. Most of the stages confirmed by FT-IR only; based on their functional group Interconversion characteristics, because these

intermediates having well-known chemical structures and the rest of the compounds where ever required were characterized with the support of all spectral evidence.

1H-indole-5-carbonitrile (5): A mixture of 5-bromo-1H-indole (**6**) (100gm, 0.510 moles), copper (I) iodide(68.5 gm, 0.765moles) and N,N-Dimethyl formamide (400 mL) was taken In a 1000 mL round bottom flask under gentle stirring. Heated the reaction mixture to 145-150^{0}C for 6-8 hours. After completion of the reaction over TLC monitoring (10% methanol in Chloroform), the reaction mass was quenched in 15% Aqueous Ammonia solution and then the layer was extracted with ethyl acetate (3X 150mL). The combined organic layers were washed with saturated brine solution and dried over anhydrous sodium sulfate (10gm). The dried organic layer was distilled under reduced pressure to obtained desired 1H-Indole-5-carbonitrile[5] (5) as a light brown color solid with purity 98% and yielded (54.3 gm) 75%. FT-IR (Cm^{-1}): 3322.91, 3066.64, 2926.02, 2851.87, 2218.71, 889.23, 767.27, 664.08.; Melting range: 98-105^{0}C.

1H-indole-5-carboxylic acid (4): In a 500mL Round bottom flask taken compound 5(1H-indole-5-carbonitrile, 50gm, 0.351 moles) for base hydrolysis in 25% sodium hydroxide solution (300 mL) by heating the reaction mass to 90-95^{0}C for 3-4 hours maintenance. After reaction completion over TLC, The reaction mass adjusted its pH to 1-2 with concentrated Hydrochloric acid solution. Then a white colored solid obtained was filtered and dried to get the yield 45.34 gm (80%). FT-IR (Cm^{-1}):3359.36, 2983.01, 2854.63, 1667.12, 1610.86, 1437.07, 1420.10, 1333.18, 1300.35, 751.30.; Melting range: 198-205^{0}C.

Methyl 1H-indole-5-carboxylate[6] (3): To a 500mL round bottom flask added 1H-indole-5-carboxylic acid (4) (42gm, 0.260 moles), Potassium carbonate (37.8gm, 0.273 moles) and Methyl iodide (47.71gm, 0.336 moles) in N,N-Dimethylformamide (84 mL). Reaction mixture was maintained for 3-4 hours at room temperature and then added DM water (198 mL) to quench the reaction. Filtered the obtained solid and dried. 29.67gm yielded with 65%. **FT-IR** (**Cm^{-1}**):3319.18, 3110.55, 2950.07, 1695.09, 1612.13, 1435.29, 1290.61, 1273.79, 1199.46, 758.39.; Melting range: 120-125^{0}C.

Methyl 3-(aminoformyl-N, N-dimethylform)-1H-indole-5-carboxylate (2): In a 1000 ML round bottom flask fitted with inert atmosphere, the compound **3** (25.00g, 0.143mol) was taken in anhydrous diethyl ether (375 mL). The reaction mixture was cooled to 0-5^{o}C and then Oxalyl chloride (23.41g, 0.185mol) was dissolved in anhydrous diethyl ether (50 mL)

was added drop wise. Then, the mixture was stirred for one hour by keeping the temperature of the process at 0-5^0 C, and then, stirring was maintained for another one hour at room temperature. A yellow precipitate was formed, which was filtered and washed with diethyl ether (2X50 mL), yielding 30.50g of the product. In another 1000 ML round bottom flask, a solution of Dimethyl amine (150.0 mL) in H2O (450 mL) was prepared, the yellow solid obtained was added, and the mixture was stirred for 15 hours at room temperature. Then, the solid was filtered, washed with water (200 mL) and dried, yielding 18g (60%) of **2**. **FT-IR** (**Cm^{-1}**):3256.57, 3119.43, 3046.19, 2951.77, 2895.07, 1707.25, 1635.25, 1622.47, 1440.01, 1283.27, 1237.89, 1121.87, 767.23. ; Melting range: 215-220^{0}C.

(3-(2-(dimethylamino) ethyl)-1H-indol-5-yl) methanol (1): In a 5000 mL round bottom flask taken 70% vitride solution in Toluene (650mL) in Diisopropyl ether (2300mL) and the solution was stirred for 20 minutes. Heated the reaction mass temperature to 40-45^{0}C and then, added Methyl 3-(aminoformyl-N, N-dimethylform)-1H-indole-5-carboxylate (**2**) (65gm, 0.237 moles) portion wise and the reaction temperature slightly exothermic to 60^{0}C. Tetrahydrofuran (325 mL) was slowly added to the reaction mass at 60^{0}C and then heated to reflux for 3-4 hours. After completion of the reaction, the reaction mass was cooled to 0-5^{0}C and then, 2N sodium hydroxide solution (100mL) was added slowly. Raised the temperature to room temperature after addition of water (600 mL), separate the organic layer and aqueous layer was extracted Diisopropyl ether (2 X 200mL). The combined organic layers were washed with saturated brine solution (150mL) and dried over anhydrous sodium sulphate. Concentrate the organic layer under reduced pressure and recorded the yield 60%, 30 gm. Spectral Characterization compound **1**: **^{1}HNMR:** δ10.69 (1H, S),δ7.41(1H, S), δ7.24(1H, d), δ7.10(1H, d), δ7.02(1H, d), δ4.97(1H, bt), δ4.53 (2H, S), δ2.89(2H, t), δ2.53(2H, d), δ2.21(6H, S).; **^{13}NMR:** 135.41, 132.21, 126.99, 122.63, 120.61, 116.38, 112.39, 110.91, 73.88, 63.94, 60.01, 58.00, 45.07, 23.08.; **Mass** (m/z):218.14, (M+H): 219.11; **FT-IR** (**Cm^{-1}**): 3400.05, 2853.97,1459.71, 1377.30, 1061.23, 721.98.

SUPPORTING CHARACTERIZATION DATA

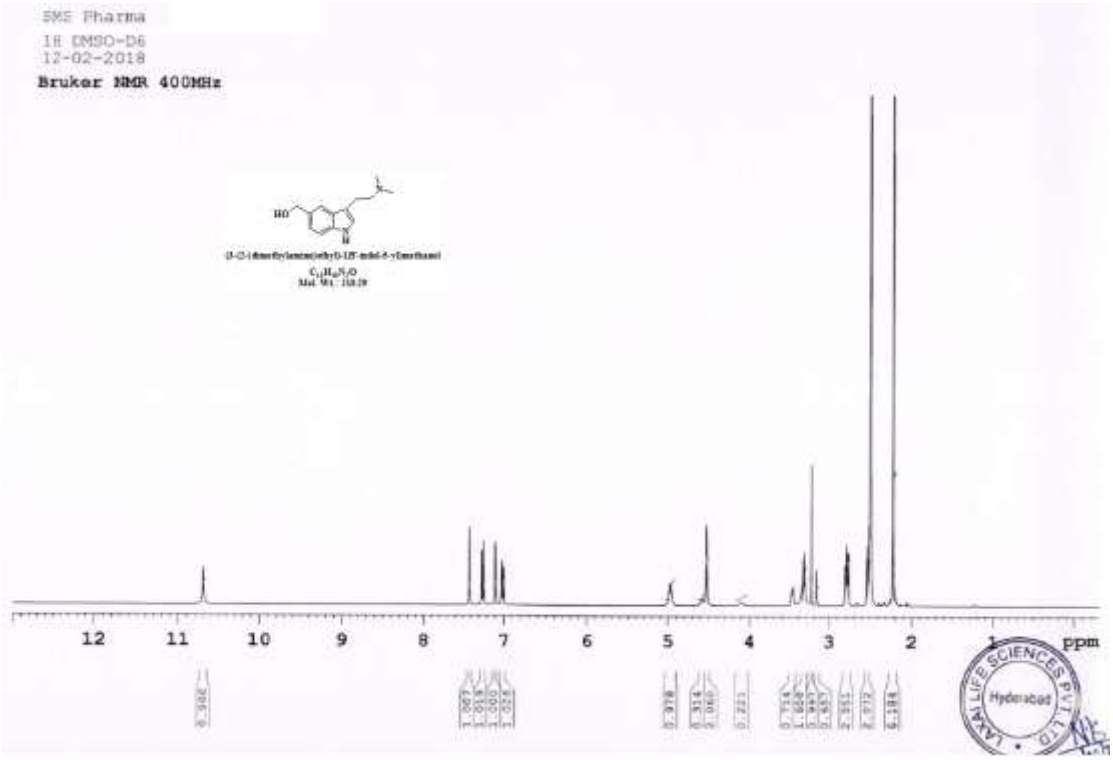


Figure 1: 1H NMR spectra of compound 1.

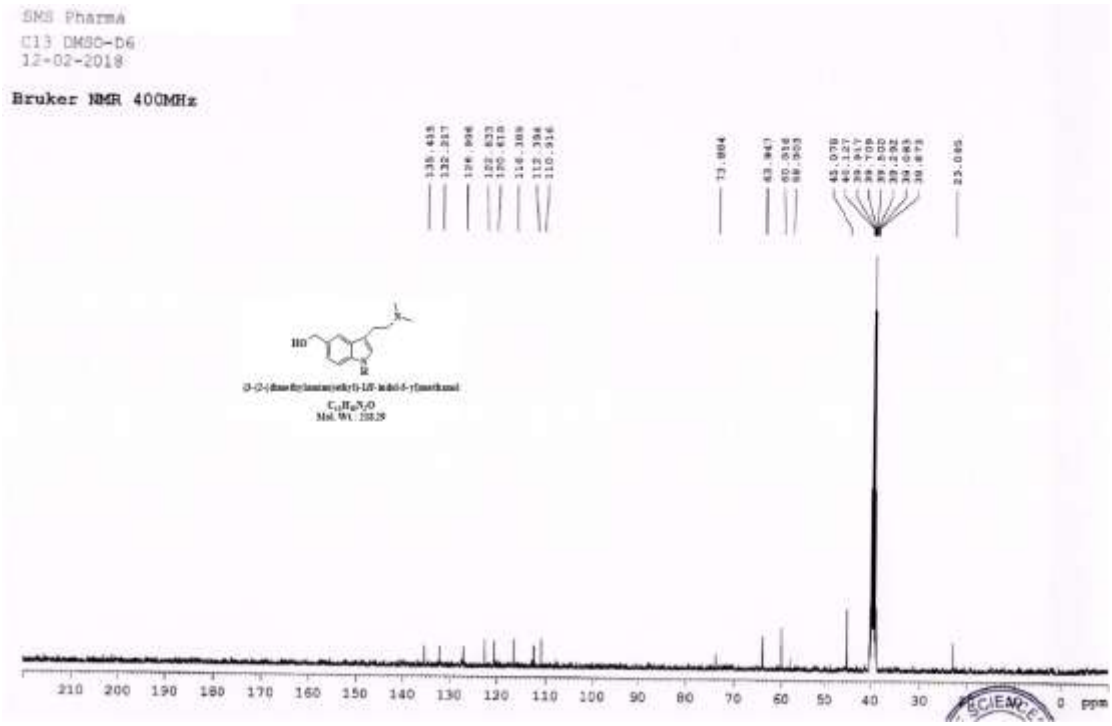


Figure 2: 13C NMR spectra of compound 1.

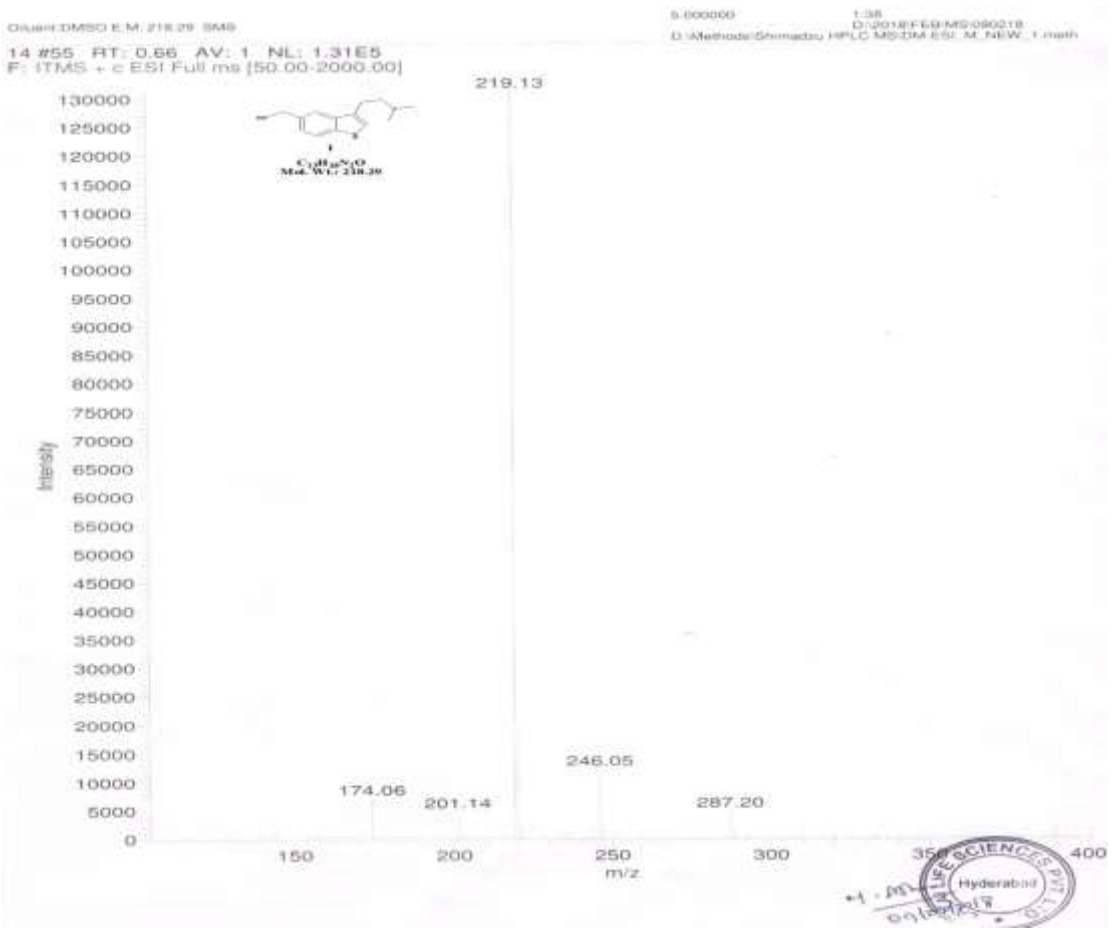


Figure 3: Mass spectra of compound 1.

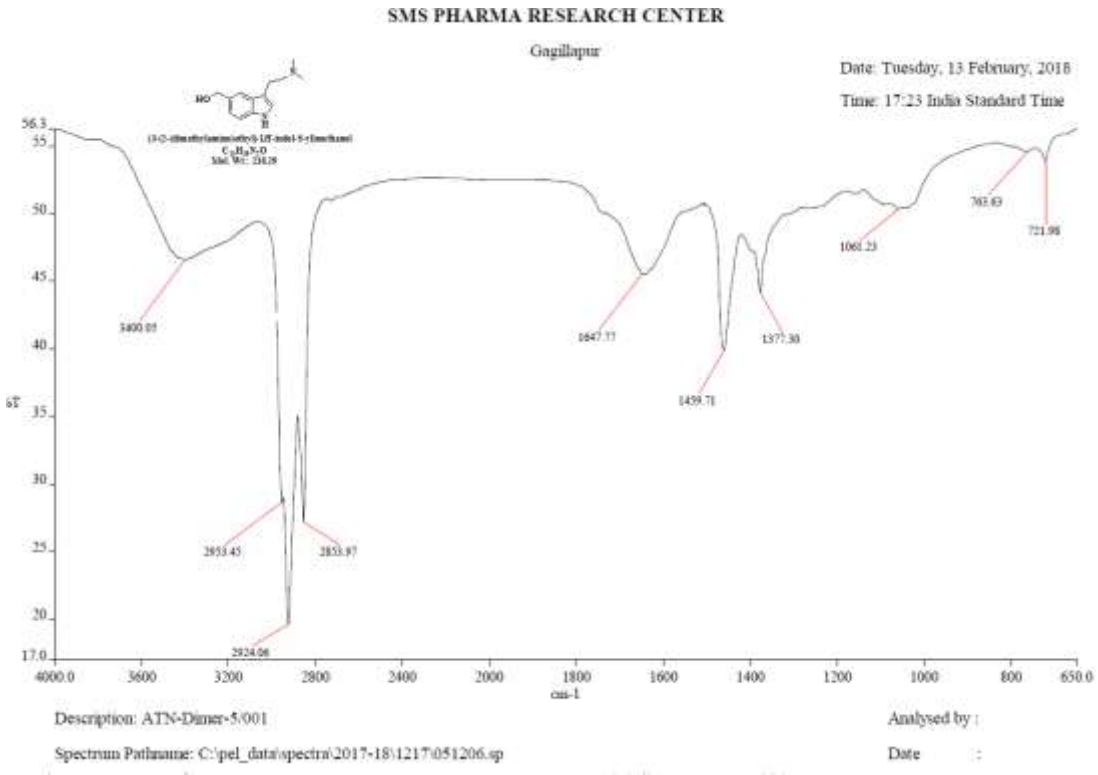


Figure 4: FT-IR spectra of compound 1.

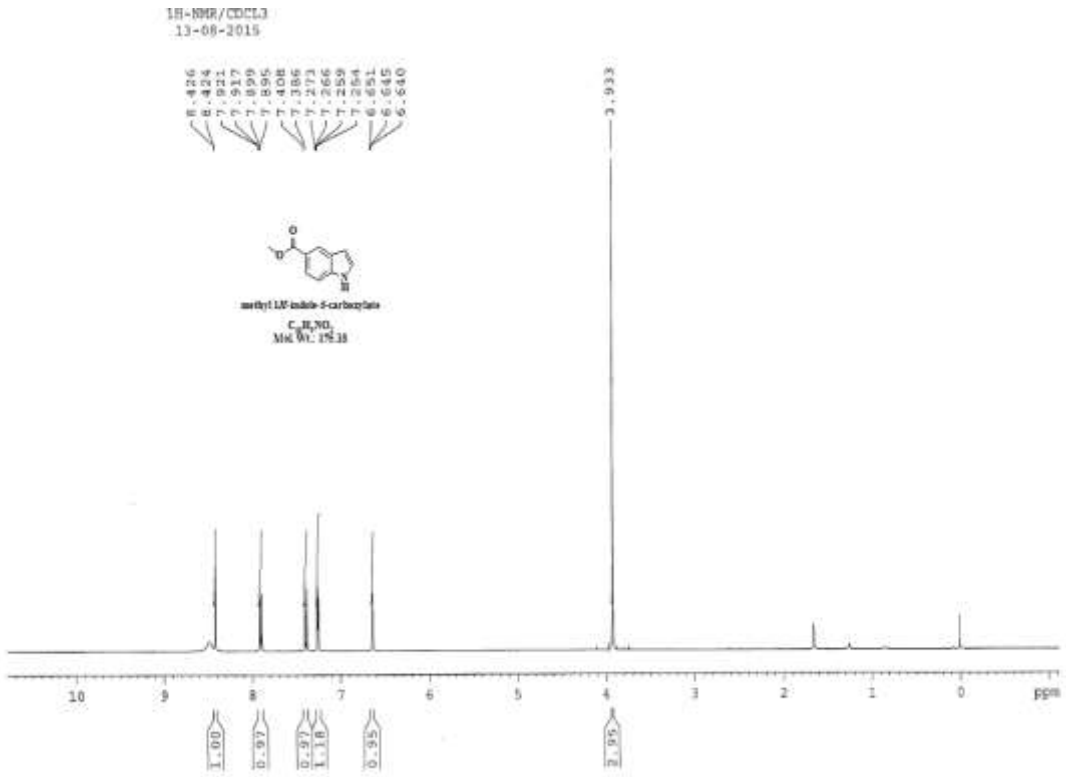


Figure 5: 1HNMR spectra of compound 3.

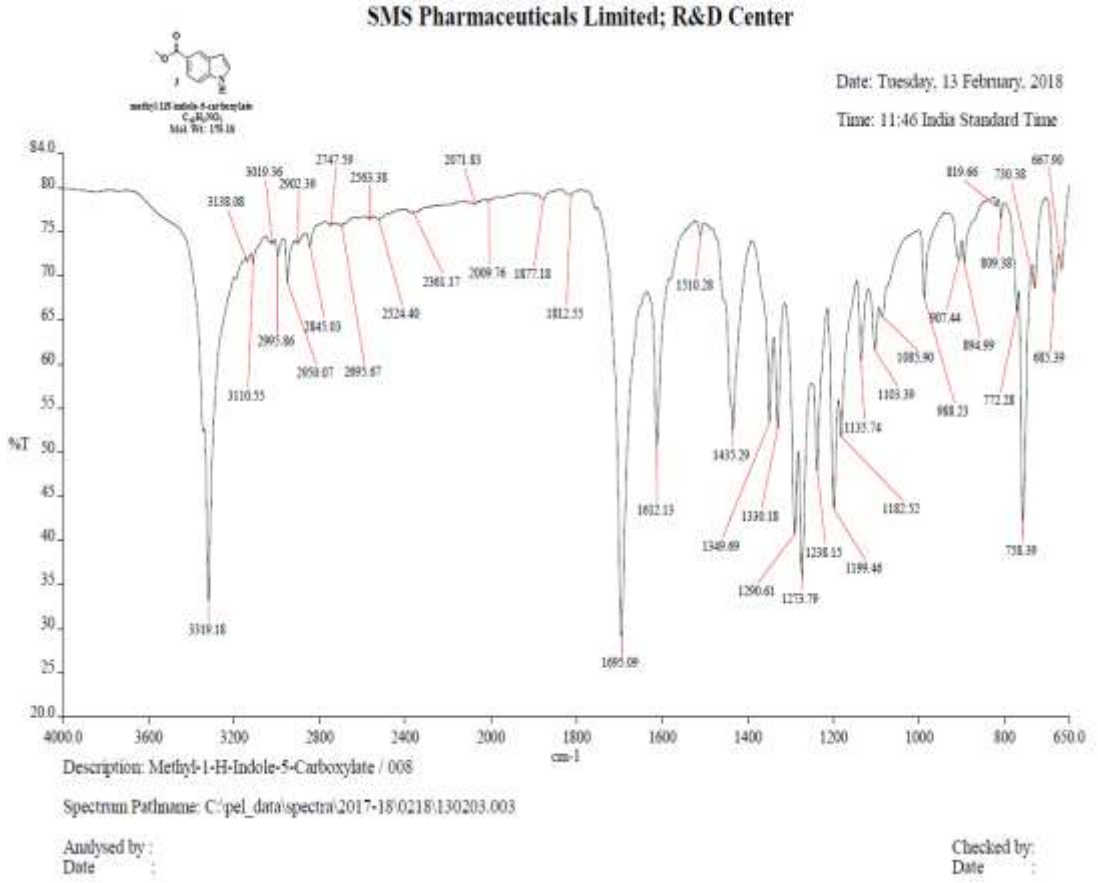


Figure 6: FT-IR spectra of compound 3.

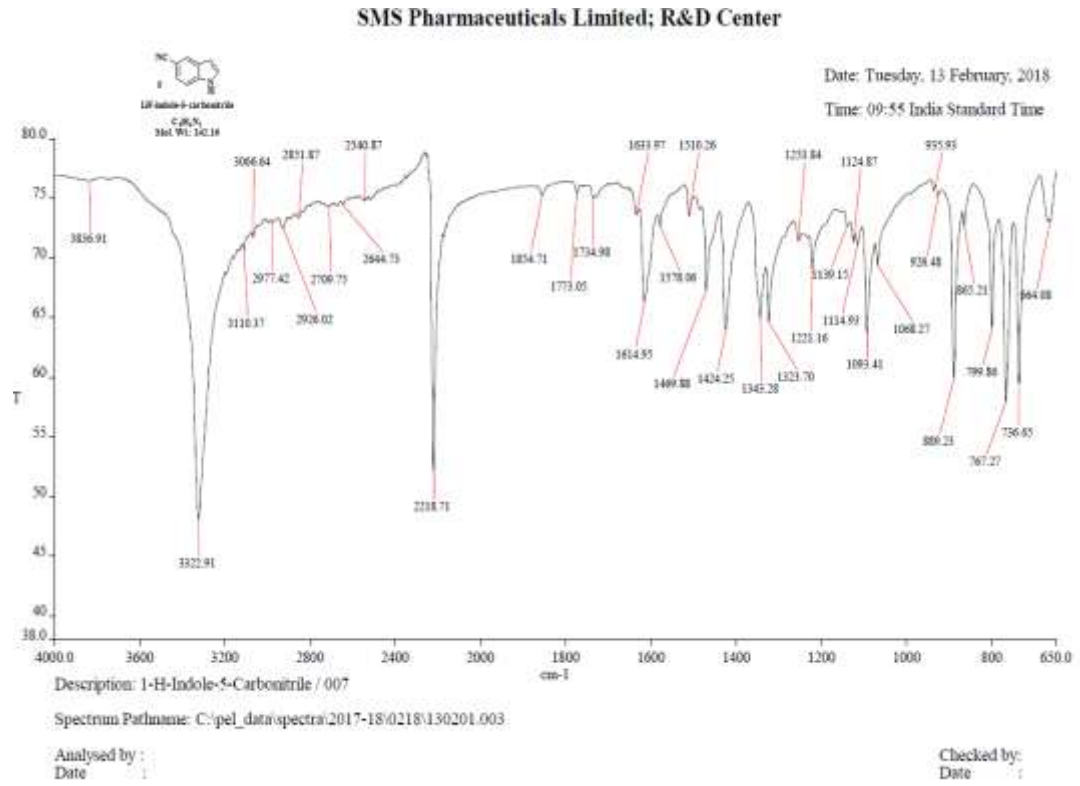


Figure 7: FT-IR spectra of compound 5.

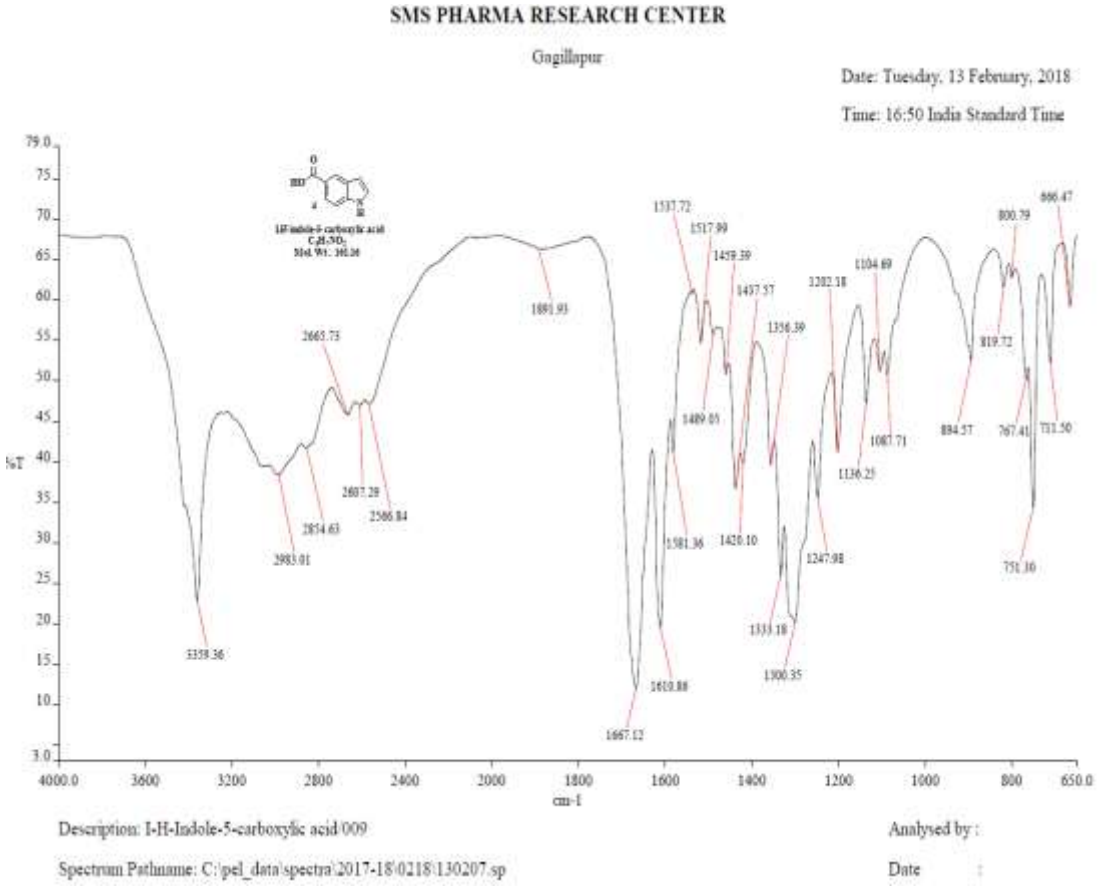


Figure 8: FT-IR spectra of compound 4.

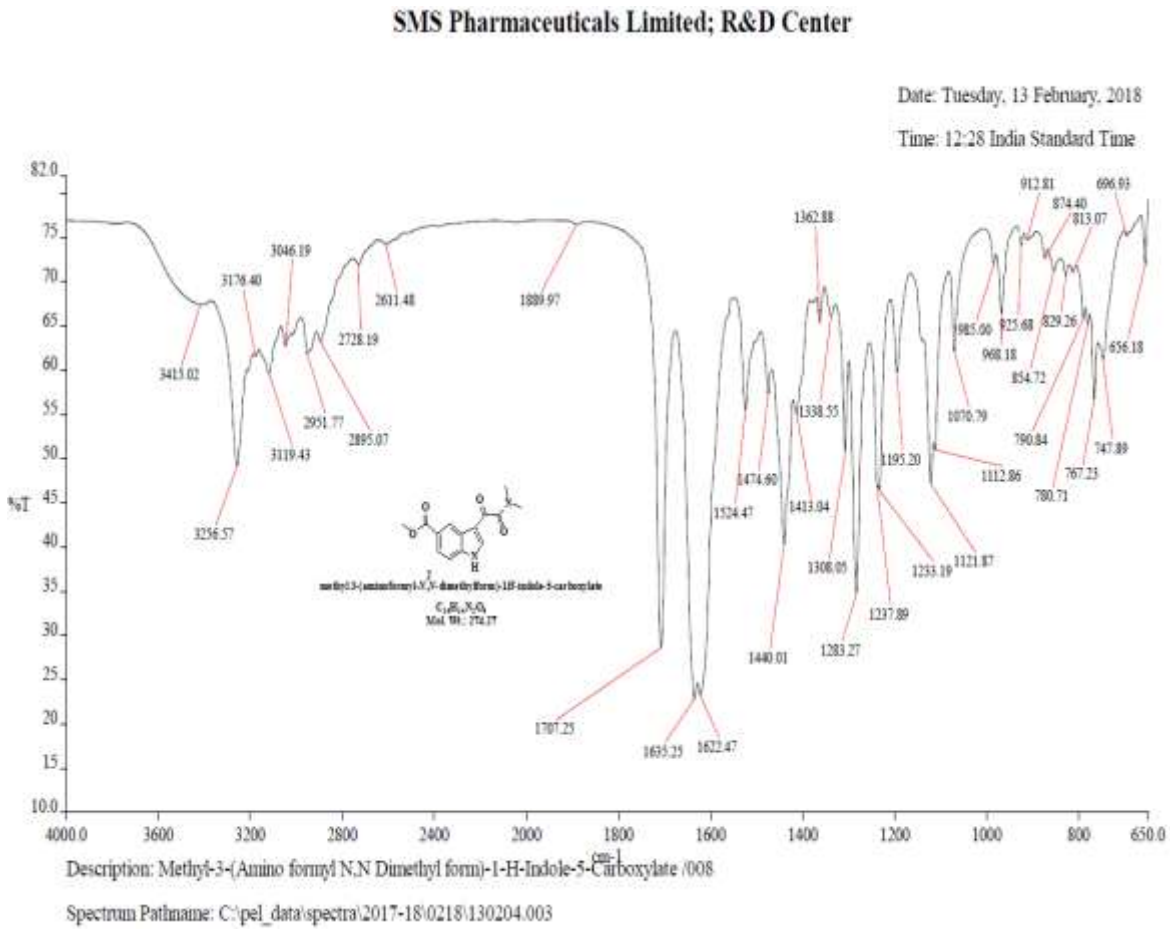


Figure 9: FT-IR spectra of compound 2.

CONCLUSION

Developed a commercially viable and cost effective process for synthesis of 3-(2-(dimethylamino) ethyl)-1H-indol-5-yl) methanol by introducing a non-pyrophoric, safety reducing agent known as Vitride. Being the targeted product is having broad range of industrial applications in the manufacturing of Triptan class of active pharmaceutical ingredients. This research can helpful to synthesis maximum number of commercial products, which are having multiple carbonyl functional groups tends to simultaneous reduction at a time.

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