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SYNTHESIS OF 1-({7-METHOXY-2-[4-(METHYLSULFANYL) PHENYL]-1-BENZOFURAN-5-YL}-N-[(N-ETHYLPYRROLIDIN-2-YL) METHYL]METHANAMINE BY REDUCTIVE AMINATION

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ABSTRACT :
Vanillin undergoes sequence of reaction forming phosphonium salt through dimethyaminomethyl derivative (Mannich reaction). The synthesis of phosphonium salt can be achieved by sequence of three steps. A solution of Mannich base in acetic anhydride was refluxed for 24 hrs to give crude diacetate which is purified and treated with HCl to give chloromethyl derivative. It is further treated with triphenylphosphine in dry benzene under reflux condition. The phosphonium salt undergoes condensation with 4-methylsulfanylbenzoyl chloride by refluxing in toluene in presence of triethylamine. The reaction was completed in 6 hrs. The crude product was purified by using column chromatography. The resulting 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde was subjected to reductive amination and the final product 1-({7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}-N-[(N-ethylpyrrolidin-2-yl)methyl]methan amine was purified by column chromatography and characterized by FT-IR, NMR and Mass spectroscopy.

KEY WORDS :- Vanillin, Mannich reaction, Benzofuran, Reductive amination, 4-methylsulfanylbenzoyl chloride.

INTRODUCTION:

Large numbers of methods are reported for the synthesis of 2-alkyl/2-arylbenzofurans derivatives. 2-(2-Methoxyaryl)-1-arylethanone derivative[III] when subjected to hydrogenation by passing hydrogen gas in presence of palladium on charcoal in ethanol containing hydrochloric acid forming 2-arylbenzofuran. In an alternative approach, 2-(2-Methoxyaryl)-1-arylethanone derivative are cyclised using HI in acetic acid or using some other acids to give the 2-arylbenzofuran[I,II]. Another route involves[IV] cyclisation via condensation reaction of phenacyl phenyl ether by using PPA in xylene at 130^0C or same condensation has been carried out by using acids[V] to forming 2-arylbenzofurans. The most commonly used approach[VI] for the synthesis of 2-arylbenzofuran was the coupling of cuprous aryl acetylenes with o-halophenols in pyridine under reflux conditions. The aryl acetylenes were treated with o-halophenols in

presence of Cu(I) iodide and triethylamine using $(PPh_3)_2PdCl_2$ as a catalyst also forming 2-arylbenzofurans[VII]. During this conversion, reaction can also proceeds through cuprous aryl acetylenes. The benzofuran was undergoes arylation[VIII] at 2-position by using arylmercuric halide in presence of Li_2PdCl_4. But this approach for the synthesis of 2-arylbenzofuran was not conveniently used because of poisonous mercuric by-products. Another photolytic synthesis approach has also been used for the synthesis of 2-arylbenzofuran. β,β-Bis-(o-methoxyphenyl)vinylbromides undergoes photolysis[IX] in presence of benzene to furnish 2-arylbenzofuran. Benzyloxybenzaldehydes[X,XI,XII] were obtained by the benzylation of substituted salicyladehydes (ortho position was not substituted) on reaction with sodium methoxide in DMF under reflux conditions forming 2-arylbenzofuran. In another approach, benzyloxybenzaldehydes are refluxed with potassium carbonate in methanol to obtain 2-arylbenzofuran.

There are literature known forever for the synthesis of 2-arylbenzofuran from 2-hydroxystilbenes. One of the approach[XIII] involves the reaction of 2-hydroxystilbenes with lead tetraacetate in benzene at cold condition (temperature should be maintained at 17-18^{0}C) forming 2-arylbenzofuran. In another approach[XIV], the protected 2-hydroxystilbenes were subjected to hydrogenation followed by the oxidation (aromatisation) using DDQ to 2-arylbenzofuran. In some known synthesis of 2-arylbenzofuran, intramolecular condensation of Wittig reagent was used. o-Acyloxybenzylidene phosphoranes undergoes intramolecular condensation[XV] in presence of base in toluene under reflux conditions. Nayak and Banergi have been achieved[XVI] the synthesis of 2-arylbenzofuran from o-aryloxy acetophenones using titanium (IV) chloride and zinc in dioxane under reflux conditions. o-Methoxybenzoins[XVII] in presence of excess of 47% of hydroiodic acid in glycial acetic acid undergoes demethylation and cyclisation to 2-arylbenzofuran. For the synthesis, copper acetylide approach has been widely used for the synthesis of 2-arylbenzofuran-5-carbaldehyde involving either multistep sequence of reactions with low yield of end product.

The two most commonly used direct reductive amination methods are differ in the nature of reducing agent. The first method is catalytic hydrogenation with metals such as platinum, palladium, nickel, etc catalyst[XVIII,XIX]. This is economical and effective reductive amination method, particularly in large scale reactions. But such reactions may give the mixture of products and low yields depending on the molar ratio and structure of the reactant[XX]. Hydrogenation has limited use with compounds having other reducible groups such as carbon-carbon multiple bonds and other groups like ester, nitro[XXI,XXII], cyano[XXIII], etc groups. These metal catalysts may be inhibited for the starting materials containing divalent sulfur[XXIV,XXV].

The second method utilizes hydride reducing agents particularly sodium cyanoborohydride ($NaBH_3CN$) for reduction[XXVI,XXVIII]. The sodium cyanoborohydride is successfully used because of its stability in relatively strong acidic conditions (~ pH = 3) and higher stability in hydroxylic solvents such as methanol. It has different selectivities at different pH scale[XXVII]. At pH = 3-4, it reduces ketones, but this become slow at higher pH. At pH 6-8, the more basic imines are protonated preferentially and reduces faster than aldehydes and ketones[XXVII].

The other hydride reducing reagents reported for the reductive amination are- boron-pyridine (BH_3-Py)[XXIXa], $Ti(O^iPr)_4/NaBH_3CN$[XXIXb], borohydride exchange resin[XXXIa], Zn/AcOH[XXXIb], $NaBH_4/Mg(ClO_4)_2$[XXXIc], $Zn(BH_4)_2/ZnCl_2$[XXXId], etc. Some reports of electrochemical reductive amination has been also reported[XXXII]. After surveying many commercially available hydride reducing reagents, sodium triacetoxyborohydride $[NaBH(OAc)_3]$[XXX] is the mild reducing reagent and exhibits remarkable selectivity as a reducing agent. It reduces aldehydes selectively over

ketones[XXX], except β-hydroxy ketones which reduces selectively to 1,3-trans-diols. The steric and strong electron withdrawing effect of three acetoxy groups stabilizes boron-hydrogen (B-H) bond and responsible for its mild reducing property (because of its more stability) and selectivity[XXVIII]. Direct reductive amination is carried out in 1,2-dichloroethane (DCE) under standard reaction conditions [Mixture of the carbonyl compound and amine (0 to 5% molar excess) in 1,2-dichloroethane stirred with 1.3 to 1.6 equivalent of [$NaBH(OAc)_3$] under dry atmosphere[XXXIII].

Reductive amination is one of the versatile method for the synthesis of secondary or tertiary amines from aldehydes or ketones by using suitable reducing agent in one-pot fashion. The 2-aryl-7-methoxy-benzofuran-5-carbaldehyde has been treated with various primary amines in presence of sodium triacetoxyborohydride (as reducing agent) forming secondary amines containing benzofuran nucleus. This reaction has been carried out at room temperature and in acidic medium (by using acetic acid).

RESULTS AND DISCUSSION:

We thought of utilizing the Mannich reaction for the synthesis of 2-hydroxybenzyl chloride derivative which is further converted into Wittig reagent (triphenylphosphonium salt). It is then converted into arylphosphonium ester of aromatic or aliphatic acid by using acid chloride in presence of base followed by in situ subjected to intramolecular Wittig reaction for the cyclisation (formation of furan ring). Though the intramolecular Wittig reaction has been used for the synthesis 2-arylbenzofurans, only the synthesis of 2-alkyl/aryl-5-formyl-1-benzofuran synthesis was reported[XXXIV]. During the Wittig carbonyl olefination, ester functional group even less reactive than aldehyde and ketone functional group, in our approach we can visualizing that phosphorane might react with ester carbonyl in intermolecular fashion in presence of aldehyde functional group.

The phosphorane salt (**3**) required for the synthesis of 2-aryl/alkyl-5-formyl-7-methoxy-1-benzofuran (**5**) was synthesised form easily available starting material vanillin (1). We have carried out Mannich reaction of vanillin for the synthesis of 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde[XXXIV] by using dimethylamine (40%) and paraformaldehyde (37%) in methanol at room temperature. This synthesis was already carried out Sinhababu and Borchard[XXXV] by treating vanillin with dimethylamine and formaldehyde in ethanol. The next step of the synthesis was the formation of 2-hydroxy-5-formylbenzyl chloride derivative which is used for the synthesis of Wittig reagent. The Mannich base was then acetylated by refluxing it with acetic anhydride for about 24 hrs and the volatile material was distilled out under reduced pressure to give crude diacetate. It is not purified further and directly treated with conc. Hydrochloric acid to gives 2-hydroxy-5-formylbenzyl chloride derivative in good yield. During this reaction, we have been used pure acetic anhydride. This benzyl chloride derivative on reaction with triphenyl phosphine in dry benzene under reflux condition forming phosphonium salt (Wittig reagent) (3) m.p. 254^0C (decompose). This phosphonium salt formed was either reacted with aldehyde functional group or not con be confirmed by carring out suitable test of aldehyde functionality of phosphonium salt. It can be shows positive neutral $FeCl_3$ test (phenolic OH group) and 2,4-DNP test (aldehydic carbonyl group) indicates the presence of unreacted aldehyde functionality. These groups are also confirmed by recording FT-IR spectra. In its IR (KBr) spectrum, it showed a band at 3450-3350 cm^{-1} (due to presence of phenolic OH group) and 1695-1685 cm^{-1} (due to carbonyl group of aldehyde).

The key step for this synthesis was the condensation of phosphonium salt with acid chloride in presence of base (intramolecular Wittig reaction). The acid chloride required for the synthesis was available in the college laboratory or synthesised by the chlorination using thionyl chloride and then directly used for the reaction without purification. The acid chloride was then treated with phosphonium salt in toluene in presence of triethyl amine as base under reflux conditions (5-8 hrs, depending on the nature of acid chloride carbonyl group). Pour the organic layer in cold water to remove the ionic impurity formed during the reaction i.e. triethylammonium hydrochloride. The organic layer was dried by washing it with brine water (saturated sodium chloride solution, by osmosis phenomenon) and finally dried by anhydrous sodium sulphate. Distilled out the solvent under reduced pressure and the crude product obtained during this reaction was sticky solid, so that it can be recrystallized or purified by column chromatograpy (by using 230-400 mesh silica) by using 30-40% ethyl acetate in petroleum ether as mobile phase.

The formation of the product (**4**) and its structure has been confirmed from the analytical data, FT-IR (KBr), NMR and mass spectroscopy. Absorption frequencies at 2973, 2938 and 2834 cm^{-1} are due to the aromatic C-H bonds stretching vibrations of both aromatic and heterocyclic ring. These bands are weak due to small change in dipole moment due to vibrations. The frequencies at 2723 and 1691 cm^{-1} are due stretching vibrations of aldehydic C-H bond and aldehydic carbonyl (C=O) bond stretching vibrations. The band due to carbonyl vibration is strong and sharp band because of large change in dipole moment due to stretching. The frequencies at 1648 and 1592 are due to vibrations of aromatic C=C bonds.

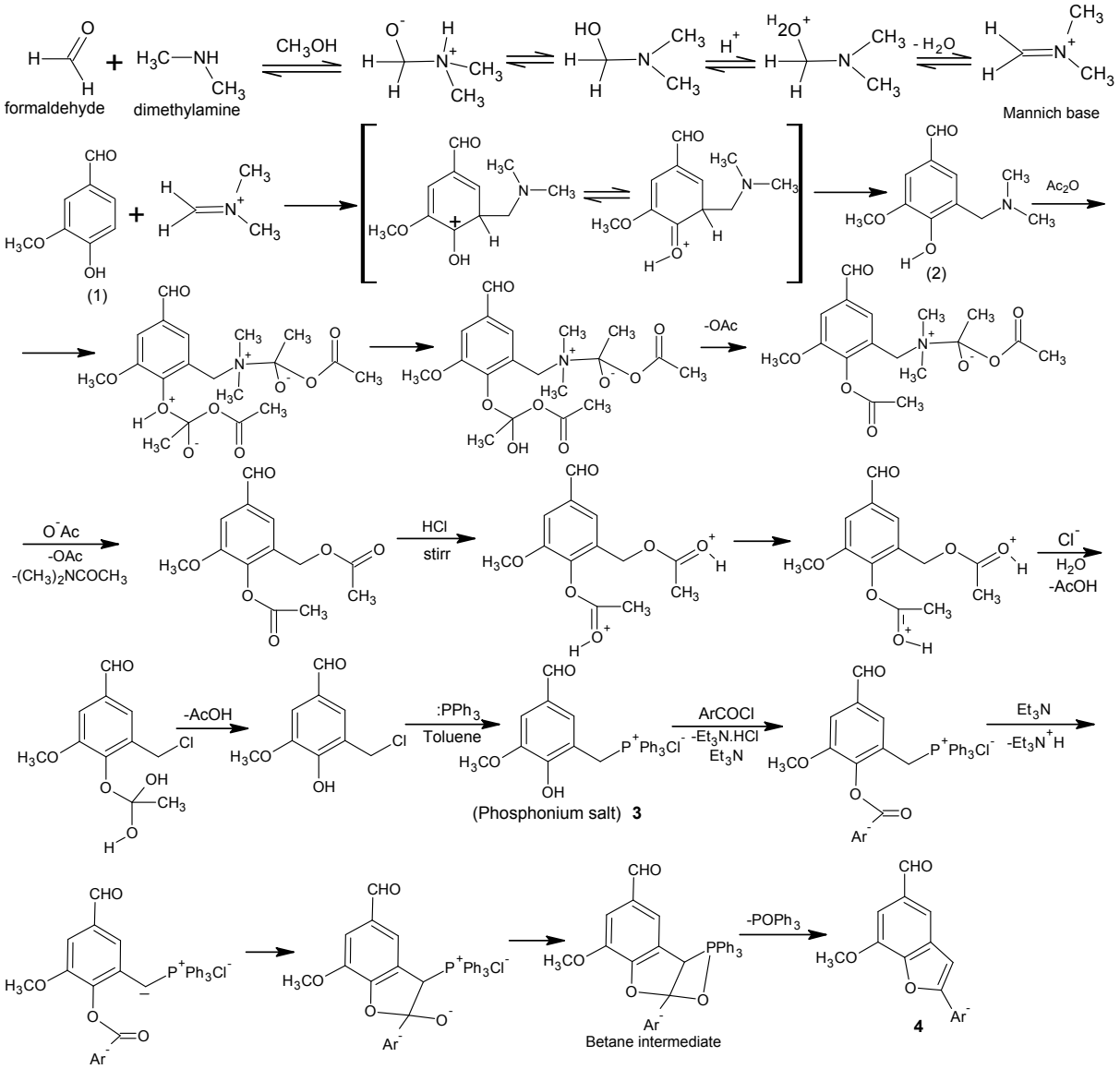
The NMR spectra of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde **(4)** was recorded in deuterated DMSO as solvent, TMS as reference and in 300 MHz instrument. The singlet at 2.532 of three protons is due to thiomethyl group attached to aromatic ring. The chemical shift value indicates that, methyl protons are deshielded due to – I effect of sulphur atom. The singlet at 4.089 is due to three protons of methyl group attached to oxygen atom i.e. methoxy protons. The aromatic protons shows chemical shift in the region of 7.04 – 7.78 ppm. The proton of C_3-H of furan ring shows singlet at 7.040. The aldehydic proton shows singlet at 9.997 ppm. It is highly deshielded due to anisotropic effect of aldehydic carbonyl (C=O) group and – I effect of aldehydic oxygen atom. In mass spectrum, it shows (M + 1) peak at 298.94 and (M + 2) peak at 299.92 with $1/3^{rd}$ intensity indicates presence of one sulphur atom in the compound.

7-Methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (**4**) is treated with 2-(N-ethylpyrrolidin)methanamine in dichloroethane (as solvent) in acidic medium at room temperature in presence of sodium triacetoxyborohydride or tetramethylammonium triacetoxyborohydride. The aldehyde functionality was reacted with amines forming Schiff bases which are in situ reduced to amines in acidic medium. The product formation was confirmed by monitoring the TLC in suitable solvent. The product formed was extracted with multiple extraction by using ethyl acetate. The organic layer was washed by saturated sodium bicarbonate (to remove acidic impurities) and by brine water (to remove water from ethyl acetate, osmosis principle). The excess solvent was evaporated under reduced pressure forming 1-({7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}-N-[(N-ethyl pyrrolidin-2-yl)methyl]methanamine (**5**) solid product which was characterized by FT-IR, NMR and mass spectra & from the physical constant like m.p. The yield observed during the in situ reaction was good as compared to the amination carried out in two different steps. The aldehydic carbonyl

peak in the region of 1695-1685 cm^{-1} was disappear while new peak in the region of 3374 cm^{-1} observe in the FT-IR spectra of amine υN-H vibration indicate the formation of product. The singlet at the region of 4.01 ppm of two protons indicates the presence of Ar–**CH_2**-NH protons in NMR spectra is also confirming the formation of reductive amination product.

EXPERIMENTAL WORK:

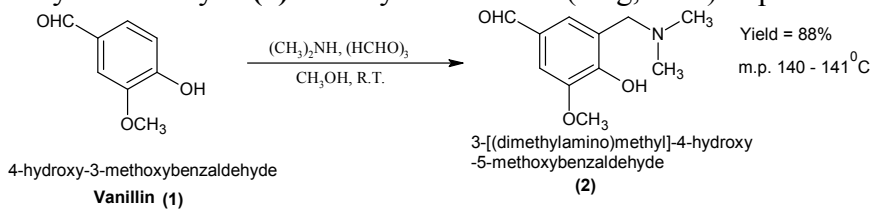
Mechanism: (Vanillin plays role of acid in Mannich reaction)



1. Preparation of 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde (2)

Vanillin **(1)** (76 g, 0.5 mol) was added to a well stirred solution of 37% aqueous paraformaldehyde (60 g, 0.75 mol) and 38% aqueous dimethylamine (90 g, 0.75 mol) in methanol (450 ml). The reaction mixture was refluxed for 30 min and the stirred at ambient

temperature for 8 hrs. It was then cooled to 5^0C and the white granular solid formed was filtered, washed with ice cold acetone (50 ml) and dried under vaccum to give 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde **(2)** as a crystalline solid (92 g, 88%) m.p. 140-141^{0}C.



4-hydroxy-3-methoxybenzaldehyde
Vanillin (1)

3-[(dimethylamino)methyl]-4-hydroxy
-5-methoxybenzaldehyde
(2)

2. Preparation of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (3)

A solution of 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde **(2)** (10 g, 0.047 mol) in acetic anhydride (50 g, 0.49 mol) was refluxed for 24 hrs. The volatile material was removed by distillation under reduced pressure. The residue crude diacetate was cooled and add concentrated hydrochloric acid (45 ml, 0,53 mol) to it gradually. The reaction mixture was stirred at about 1.5 hours at ambient temperature. The chloromethyl derivative formed was extracted by using benzene (2 x 75 ml). The combined benzene layer was washed with water (2 x 50 ml), dried over Na_2SO_4 and evaporate to gives a solid. The solid compound dissolves in benzene (125 ml) and triphenylphosphine (8 g, 0.03 mol) was added to it. The reaction mixture was heated under reflux for 6 hrs. The solid separated was filtered, washed with hot benzene (25 ml) and dried to gives (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride **(3)** (17.50 g, 79%), m.p. 254^{0}C (decomp).

3. Synthesis of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde:

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (3.5 g, 7.5 mmol), 4-(methylsulfanyl)benzoyl chloride (7.8 mmol) and triethylamine (1.6 g, 16 mmol) in toluene (70 ml) was heated under reflux for 5 hrs. The reaction mixture was cooled to room temperature and water (50 ml) was added to it. Separate the organic layer by separating funnel and wash it by water (2 x 50 ml) and dried over Na_2SO_4. Toluene was removed under reduced pressure and the residue obtained was purified by using silica column chromatography (100-200 mesh, Eluent 20% ethyl acetate in hexane), from the 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (1.385 g, 58%) as a faint yellow crystalline solid, m.p. 115 ^{0}C.

FT-IR (KBr): 2973, 2938, 2834, 2723, 1691, 1648, 1592, 1344, 1218, 1141 cm^{-1}.

NMR (300 MHz) (DMSO-D6; δ ppm) $C_{17}H_{14}O_3S$ (mol. Wt. 298.368 g/mol): 2.532 (s, 3H, SCH_3); 4.089 (s, 3H, OCH_3); 7.040 (s, 1H, Ar-H); 7.356-7.264 (m, 4H, Ar-H); 7.692 (s, 1H, Ar-H); 7.810-7.784 (d, 2H, Ar-H); 9.997 (s, 1H, CHO).

Mass Spectra: (M+1) = 298.94 and (M + 2) = 299.92.

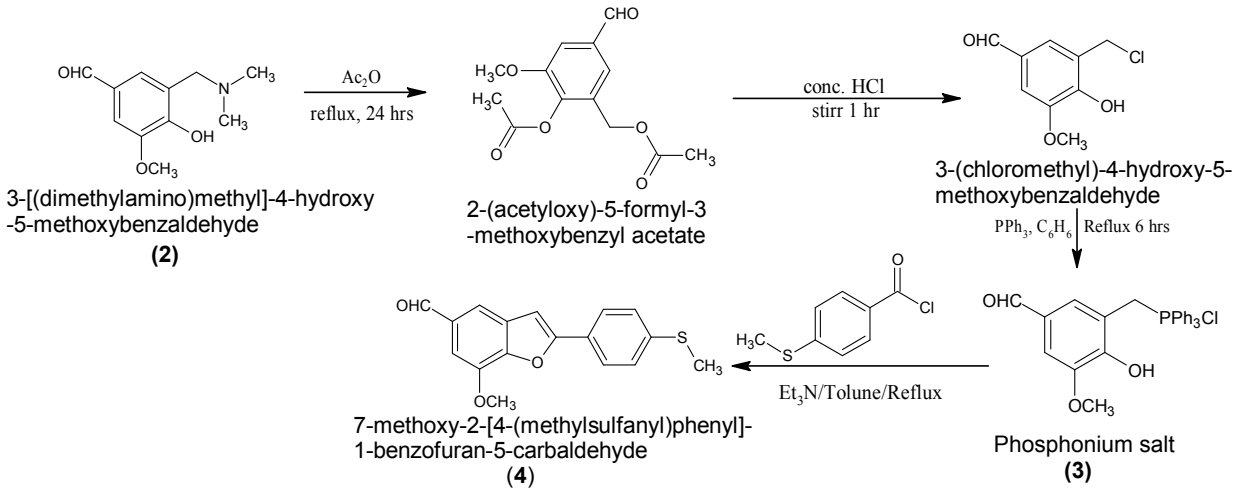


Fig 1: FTIR of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-carbaldehyde

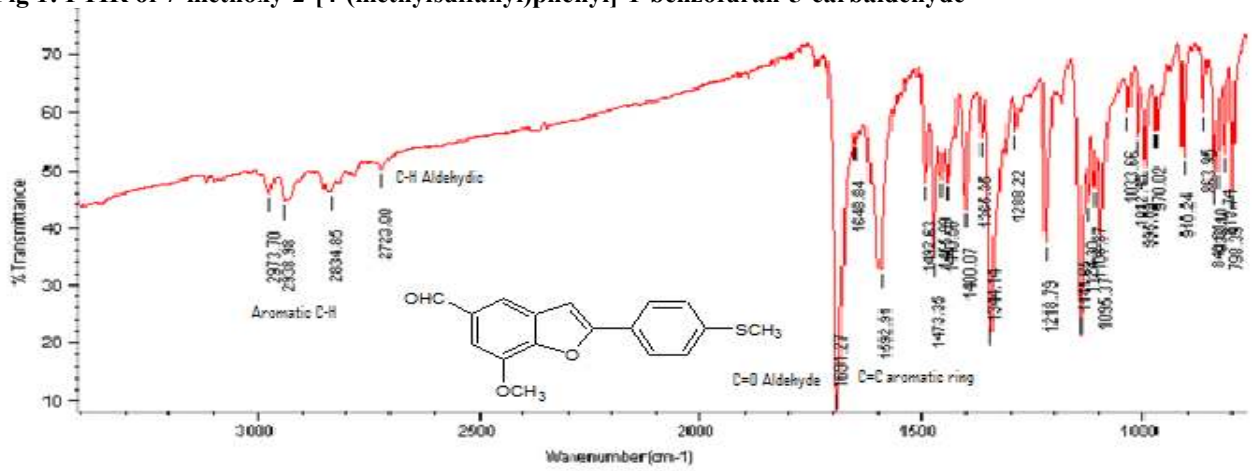
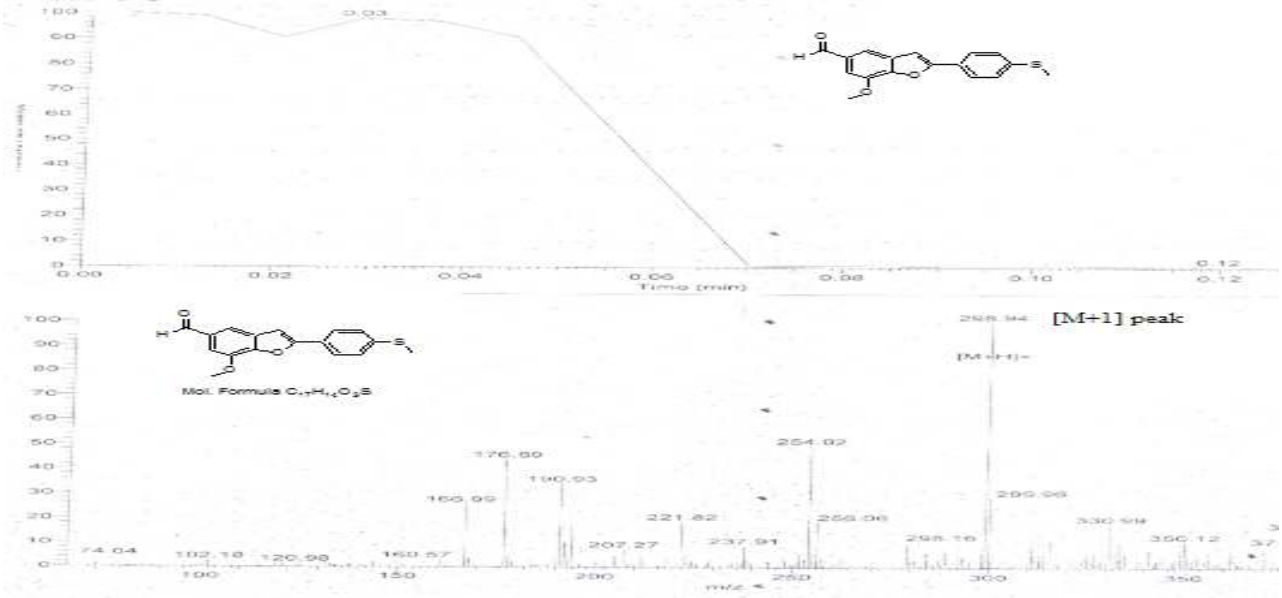
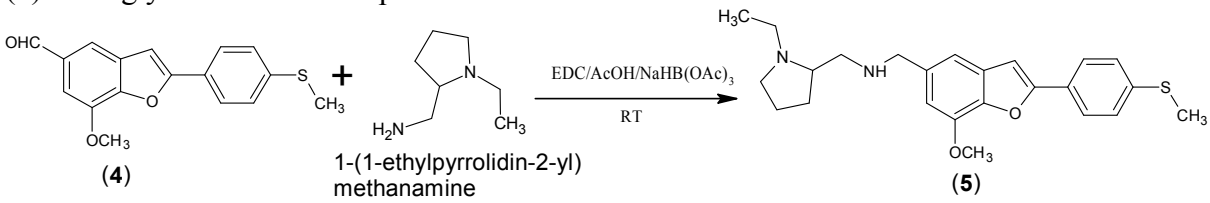


Fig 2: Mass spectra of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-carbaldehyde



4. Synthesis of 1-({7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}-N-[(N-ethylpyrrolidin-2-yl)methyl]methanamine (5):

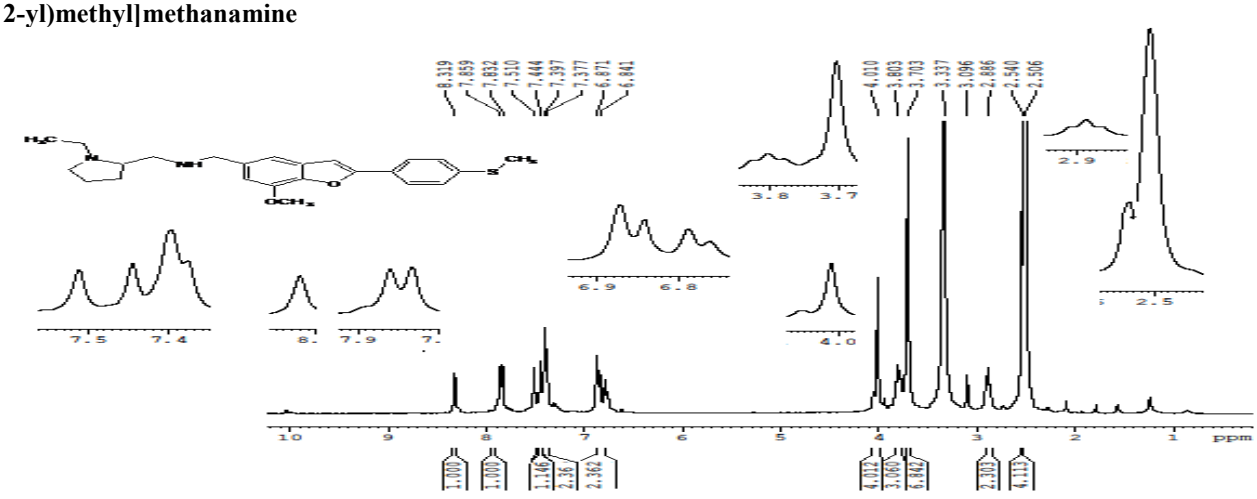
To a stirred solution of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (**4**) (0.48 mmol) and 2-(N-ethylpyrrolidin)methanamine (0.57 mmol) in ethylene dichloride (6 ml) in presence of catalytic amount of acetic acid for 6 hours at ambient temperature. The completion of reaction was confirmed by monitoring TLC time to time. After completion of reaction, add sodium triacetoxyborohydride (202 mg) and stirred the reaction mixture overnight at room temperature. Reaction mixture was quenched by saturated solution of sodium bicarbonate and product was extracted with (25ml x 2) ethyl acetate. Combined the organic layers and washed with brine (saturated NaCl), dried by using anhydrous sodium sulfate. Concentrate the organic layer and residue obtained was purified by column chromatography (silica, 100-200 mesh, Eluent 30% ethyl acetate in hexane) obtain 1-({7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}-N-[(N-ethylpyrrolidin-2-yl)methyl]methanamine (**5**) having yield 84 % and m.p 156-158 ^{0}C.



FT-IR (KBr): 3374, 1643, 1590, 1515, 1467, 1338, 1238, 1145, 1027, 825 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; δ ppm): 8.319 (s, 1H); **7.84** (d, 1H, J = 3Hz, Ar-H); 7.47 (t, 2H, Ar-H); **7.38** (d, 1H, Ar-H); 6.85 (t, 2H, Ar-H); 4.01 (s, 3H, -N-CH_2-Ar & NH); 3.80 (s, 3H, -OCH_3); 3.7 (m, 7H, 3 –NCH_2- & -N-CH-); 2.88 (s, 3H, SCH_3); 2.54 (m, 4H, 2 –C-CH_2-); 2.15 (t, 3H, -C-CH_3).

Fig 3: NMR spectra of 1-({7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}-N-[(N-ethylpyrrolidin-2-yl)methyl]methanamine



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