HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 3: (2), 2013, 163-169**

SYNTHESIS OF *N*-{[7-METHOXY-2-(4-METHOXYPHENYL)-1-BENZOFURAN -5-YL]METHYL}CYCLOPENTANAMINE BY REDUCTIVE AMINATION

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ABSTRACT:
Vanillin (**1**) 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 amino compound in acetic anhydride was refluxed for 24 hrs to give crude diacetate which is purified and reacted with HCl to give chloromethyl derivative. It is reacted with triphenylphosphine in dry benzene under reflux condition. The phosphonium salt undergoes condensation with 4-methoxybenzoyl chloride by refluxing in toluene in presence of triethylamine (Wittig reaction). The resulting 7-methoxy-2-[4-(methoxy)phenyl)-l-benzofuran-5-carboxaldehyde (**4**) was subjected to reductive amination and the final product *N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}cyclopentanamine (**5**) was purified by column chromatography and characterized by NMR and Mass spectroscopy.

KEY WORDS:- Mannich reaction, Wittig reaction, Reductive amination, Benzofuran, NMR.

INTRODUCTION

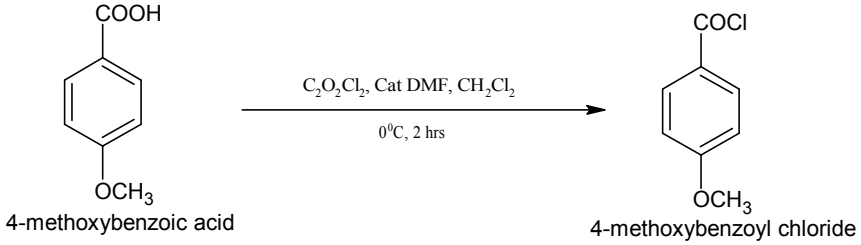
Polycyclic and or aromatic compounds containing furan ring[i], constitute a group of compounds which occurs widely throughout the plant kingdom. The origin of furan chemistry has been outlined by partington[ii]. When Scheele and coworker subjected mucic acid to dry distillation, they obtained first furan derivative, pyromucic acid known as furan-2-carboxylic acid or 2-furoic acid. Furan (1) itself was not described until Limpricht isolated[iii] it from pinewood.
2-(2-Methoxyaryl)-1-arylethanone derivative[vi] 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[iv-v].
Another route involves[vii] 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[viii] to forming 2-arylbenzofurans. The most commonly used approach[ix] for the synthesis of 2-arylbenzofuran was the coupling of cuprous aryl acetylenes with o-halophenols in pyridine under reflux conditions.

The other hydride reducing reagents reported for the reductive amination are- boron-pyridine (BH_3-Py)[xa], Ti(O^iPr)4/$NaBH_3CN$[xb], borohydride exchange resin[xia], Zn/AcOH[xib], $NaBH_4/Mg(ClO_4)_2$[xic], $Zn(BH_4)_2/ZnCl_2$[xid], etc. Some reports of electrochemical reductive amination have been also reported[xii]. After surveying many commercially available hydride reducing reagents, sodium triacetoxyborohydride [$NaBH(OAc)_3$][xiii] is the mild reducing reagent and exhibits remarkable selectivity as a reducing agent. It reduces aldehydes selectively over ketones[xiii], 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[xiv]. The direct reductive amination has been carried out in 1,2-dichloroethane (DCE), tetrahydrofuran (THF), or acetonitrile.
2-Aryl-5-formyl-7-methoxybenzofuran can be synthesized by intramolecular Wittig reaction. It undergoes reductive amination to corresponding aniline derivative.

EXPERIMENTAL WORK:
The phosphonium salt **(3)** required for the synthesis of benzofuran **(4)** was synthesized from vanillin **(1)** by the sequence of reaction shown below. The starting compound dimethylaminomethyl **(2)** was synthesized from vanillin using the procedure developed by Sinhababu and Borchardt (using dimethylamine and paraformaldehyde, Mannich reaction). The synthesis of phosphonium salt **(3)** can be achieved by sequence of three steps. A solution of amino compound **(2)** in acetic anhydride was refluxed for 24 hrs to give crude diacetate which is purified and reacted with HCl to give chloromethyl derivative. It is reacted with triphenylphosphine in dry benzene under reflux condition provided the phosphonium salt decomposed at 254^0C. The phosphonium salt **(3)** undergoes condensation with 4-methoxybenzoyl 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-methoxyphenyl]-l-benzofuran-5-carboxaldehyde **(4)** was subjected to reductive amination and the final product *N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}cyclopentanamine **(5)** was purified by column chromatography and characterized by NMR and Mass spectroscopy.

1. Synthesis of 4-phenoxybenzoyl chloride:
To a stirred solution of 4-methoxybenzoic acid (1.20 g, 7.9 mmol) in 20 ml dichloromethane, add catalytic amount of N,N-dimethylformamide followed by oxalyl chloride (ethanedioyl dichloride) (1.20 g, 9.4 mmol) at 0^0C. The completion of reaction was confirmed by monitoring TLC time to time. The reaction mixture was stirred for two hours at 0^0C. The solvent was evaporated under reduced pressure and the crude product obtained was used in further reaction.
Scheme 1:

Scheme I: Synthesis of 4-methoxybenzoyl chloride:



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

2.1. 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 (lit 139-141^{0}C).

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

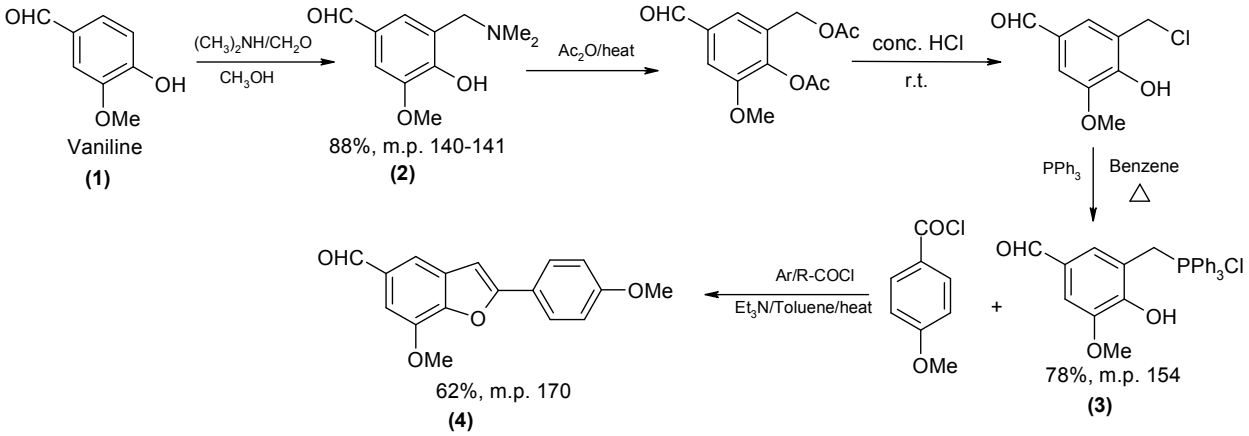
A solution of 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde **(2)** (10 g, 0.047 mol) in acetic anhydride (50 g, 0.49 mol) was refluxed for 24 hrs. The volatile material was removed by distillation under reduced pressure. The residue crude acetate was cooled and add concentrated hydrochloric 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).

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

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (3.5 g, 7.5 mmol), 4-methoxybenzoyl chloride (1.34 g, 7.8 mmol) and triethylamine (1.6 g, 16 mmol), in toluene (70 ml) was heated under reflux for 6 hrs. The reaction mixture was cooled to room temperature and water (50 ml) was added to it. Separated the organic layer by separating funnel and washed 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 40% ethyl acetate in hexane), from the 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**4**) (1.385 g, 62%) as a white crystalline solid, m.p. 170^{0}C.

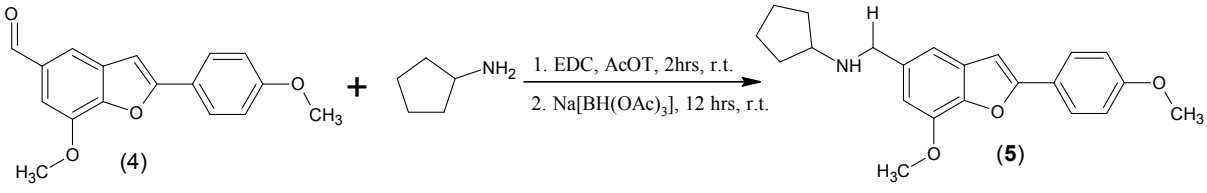
FT-IR ($\bar{\upsilon}$ in cm^{-1}): 3010, 2935, 2709, 1693, 1612, 1328, 1228, 836 cm^{-1}.
NMR (300 MHz) (DMSO-D6; δ in ppm): 10.01 (s, 1H, -CHO), 7.86 – 7.891 (m, 3H, 3 Aromatic protons), 7.42 (dd, 2H, Aromatic protons), 7.09 (dd, 2H, Aromatic protons), 4.046 (s, 3H, $-OCH_3$), 3.831 (s, 3H, $-OCH_3$).
Mass Spectra: (M+1) = 283.

Scheme II: Synthesis of 7-methoxy-2-[4-(methoxy)phenyl)-l-benzofuran-5-carboxaldehyde (4):



3. Synthesis of *N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}cyclopentanamine (5):
To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**4**) (130 mg, 0.48 mmol) and cyclopentamine (0.54 mmol) in ethylene dichloride (7 ml), add catalytic amount of acetic acid. Stirred the reaction for 2.5 hours at ambient temperature. The completion of reaction was confirmed by monitoring TLC time to time. After completion of reaction, add tetramethylammonium triacetoxyborohydride (263 mg) and stirred the reaction mixture overnight at ambient 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 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 148 mg *N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}cyclopentanamine (**5**) having yield 72% and m.p. 104-106^{0}C.

Scheme III: Synthesis of *N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}cyclopentanamine (5):



Molecular formula: $C_{22}H_{25}NO_3$**; Color:** Faint Yellow solid**; Yield:** 70%**; m.p.:** 104-106^{0}C
FT-IR (KBr): 3315, 2954, 2838, 1612, 1574, 1509, 1482, 1305, 1253, 1218, 1153, 1025, 912, 827, 744 cm^{-1}.
NMR (300 MHz) ($CDCl_3$; δ ppm): 7.887 – 7.828 (t, 2H); 7.295 (s, 2H), 7.132 (s, 1H, Furan-H); 7.085 – 7.056 (t, 2H); 4.057 (s, 2H, N-CH_2); 3.990 (s, 3H, OCH_3); 3.820 (s, 4H, OCH_3, N-CH); 3.345 (bs, NH); 1.905 (m, 2H); 1.700 (m, 4H); 1.505 (m, 2H)
Mass Spectra (m/z): 350, 351 (M+1), 352.

RESULTS AND DISCUSSION:
We have carried out Mannich reaction of vanillin for the synthesis of 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde by using dimethylamine and paraformaldehyde in methanol at room temperature. 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^{0}C (decompose). This phosphonium salt formed was either reacted with aldehyde functional group or not can be confirmed by carrying out suitable test of aldehyde functionality of phosphonium salt. It can be shown by 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 4-methoxybenzoyl 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 4-methoxybenzoyl chloride was then treated with phosphonium salt in toluene in presence of triethyl amine as base under reflux conditions. 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 was purified by column chromatograpy (by using 230-400 mesh silica) by using 35% ethyl acetate in petroleum ether as mobile phase.
In PMR (DMSO-D6) spectrum of compound **(4)** exhibited a singlet at 4.046 and 3.831 which showed the presence of two –OCH_3 group; first of benzofuran nucleus and second of 4-methoxypheny group attached at 2-position. The signal at 10.018 (singlet) indicate the presence of –CHO group. The base ion peak observed in the mass spectrum at 283.05 is due to (M + 1) fragment.
In PMR ($CDCl_3$) spectrum of compound **(5)** exhibited a singlet at 4.039 and 3.860 which showed the presence of two –OCH_3 group; first of benzofuran nucleus and second of 4-methoxypheny group attached at 2-position. The new signal observed at 3.345 (broad, singlet) indicate the

presence of –NH- group. Also the second new signal is observed at 4.057 (singlet) for two protons indicate the linkage $–CH_2$-N which is obtained by the reductive amination of aldehyde and amine. The compound **(5)** gives base ion peak at 351 is due to (M+1) fragment in its mass spectrum.

ACKNOWLEDGMENT:
The authors are grateful to the Principal and Head, Department of Chemistry, Govt of Mahrashtra, Ismail Yusuf Arts, Science and Commerce College, Mumbai 60, India, and Principal and Head, Department of Chemistry, Patkar Varde College, Goregaon (W), Mumbai, India for his constant encouragement.

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Received on February 20,2013.