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WITTIG REACTION APPROACH FOR THE SYNTHESIS OF 7-METHOXY-2-[4-ALKYL/ARYL]-L-BENZOFURAN-5-CARBOXALDEHYDE

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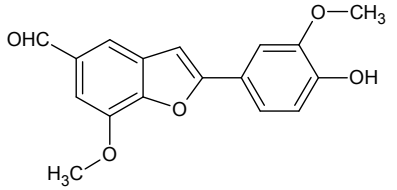
ABSTRACT:
Vanillin undergoes sequence of reaction forming phosphonium salt through dimethyaminomethyl derivative (Mannich reaction). The synthesis of phosphonium salt can be achieved by sequence of three steps which was condense with series of aliphatic/aromatic acid chlorides by refluxing in toluene in presence of triethylamine (Wittig reaction) as key step resulting 7-methoxy-2-alkyl/aryl-l-benzofuran-5-carboxaldehyde. The crude product was purified by using column chromatography and characterized by FTIR, NMR and Mass spectroscopy.

KEY WORD:- Vanillin, Mannich reaction, Intramolecular Wittig reaction, acid chloride.

INTRODUCTION

Heterocyclic compounds are highly essential to life as they play a vital role in the metabolism in plants, animals and microorganisms e.g. Purine and pyrimidine, pyroline, histidine, tryptophan, thiamine, pyridoxine, biotine, etc. This naturally occurring and some manmade showing interesting biological activities and used as key component in biological processes. The biological activities of heterocycles are due to presence of one or more heterocyclic ring. The most common heterocyclic moieties are triazoles, triazepines, quinolines, pyridines, indole, pyrrole, furan, etc.

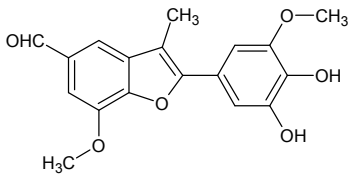
2-Aryl/alkyl-1-benzofuran carboxaldehydes are the compounds of the great interest, several of them have been used as intermediates for the synthesis of compounds possessing a wide range of biological activities. Though large number of benzofurans are isolated from natural resources, very few of them are 2-aryl-1-benzofuran-5-carbaldehyde and substituted-1-benzofuran-2-carboxylate are reported from plant sources. Thus the 2-aryl-1-benzofuran-5-carbaldehyde, eupomateriod-10 (**1**) is isolated[i] from the bark and leaves of *Eupomatia lauria*.



2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-1-benzofuran-5-carbaldehyde

(1)

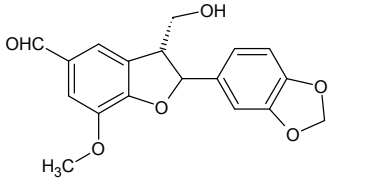
Perseal-D and Perseal-C were isolated[ii] from the leaves of *Persea obvatifolia* are shows significant cytotoxic activities against P-388, KB-16, A549, and HT-39 cancer cell lines in vitro.



2-(3,4-dihydroxy-5-methoxyphenyl)-7-methoxy -3-methyl-1-benzofuran-5-carbaldehyde

Perseal - D

(2)

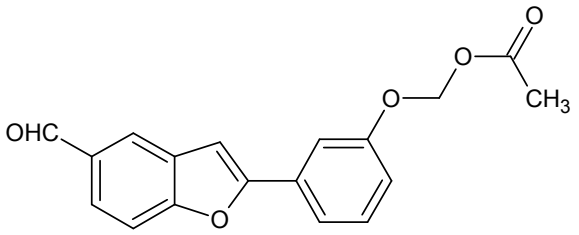


(3*R*)-2-(1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-7-methoxy-2,3-dihydro-1-benzofuran-5-carbaldehyde

Perseal - C

(3)

4-[(*E*)-2-(2-cyclopentyl-7-methoxy-1-benzofuran-4-yl)ethenyl]pyridine (**4**) having cyclopentyl group at 2-position instead of an aryl group has been used as phosphodistearase-IV inhibitor[iii]. Several 2-aryl-1-benzofuran derivatives such as (**4**) shows 5α-reductase inhibiting activity and are used for the prevention and treatment of prostatic cancer, prostatic hypertrophy, hirtotism, male pattem baldness, acne, and seborrhoea[iv].



[3-(5-formyl-1-benzofuran-2-yl)phenoxy]methyl acetate

(**4**)

We have visualized the route involving intramolecular Wittig reaction for the synthesis of 2-aryl/alkyl-7-methoxybenzofuran-5-carboxaldehyde from vanillin. The ester functional group is less reactive than aldehyde or ketone functional group in Wittig carbonyl olefination. In our work, we visualizing that the phosphorane might react with ester functionality in intramolecular fashion.

EXPERIMENTAL WORK:

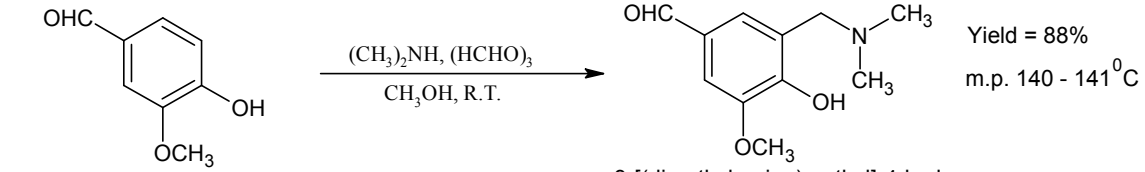
We thought of utilizing the Mannich reaction for the synthesis of 2-hydroxybenzyl chloride derivative which is further converted into Wittig reagent (triphenylphosphonium salt). It is then converted into arylphosphonium ester of aromatic or aliphatic acid by using acid chloride in presence of base followed 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[v,vi]. 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 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.

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.

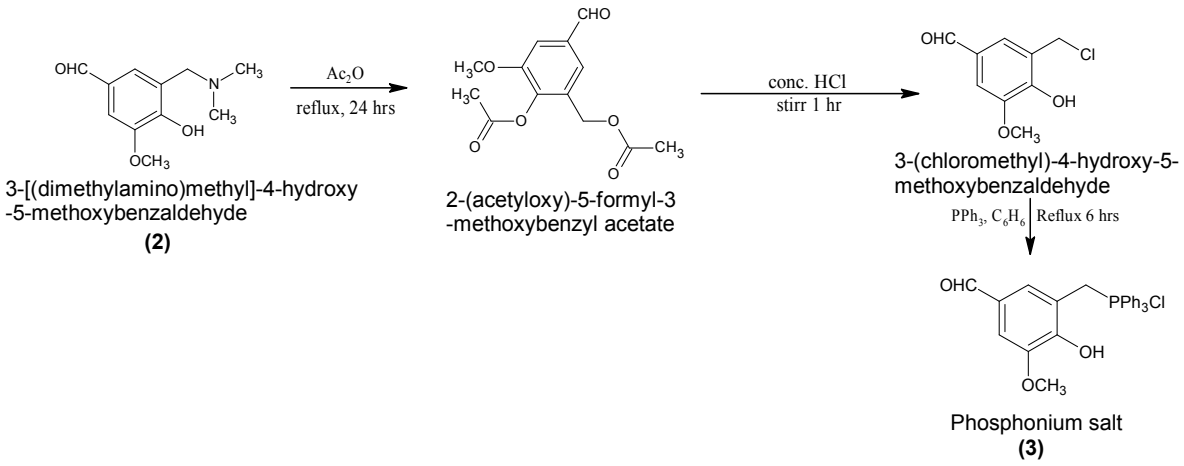


4-hydroxy-3-methoxybenzaldehyde
Vanillin (1)

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 to obtain reddish coloured solution. The volatile material was removed by distillation under reduced pressure to obtain thick reddish coloured liquid (no need to complete evaporation of acetic acid and acetic anhydride). The residue crude diacetate was cooled and add concentrated hydrochloric acid (45 ml, 0,53 mol) to it gradually (initially reaction mixture become hot by small addition of hydrochloric acid so addition should be carried out in cold water bath). The reaction mixture was stirred at about 1.5 hours at ambient temperature (during stirring colour of the solution changes to reddish brown and finally brown coloured solid separate). 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-[(dimethylamino)methyl]-4-hydroxy -5-methoxybenzaldehyde
(2)

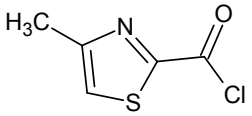
2-(acetyloxy)-5-formyl-3 -methoxybenzyl acetate

3-(chloromethyl)-4-hydroxy-5-methoxybenzaldehyde

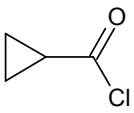
Phosphonium salt
(3)

2.1. Synthesis of acid chlorides:

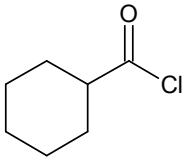
Some of the acid chlorides (5l-n) are available in our laboratory and used directly for the synthesis of benzofuran ring (Ester formation followed by Intramolecular Wittig reaction).



4-methyl-1,3-thiazole-2-carbonyl chloride
(5l)

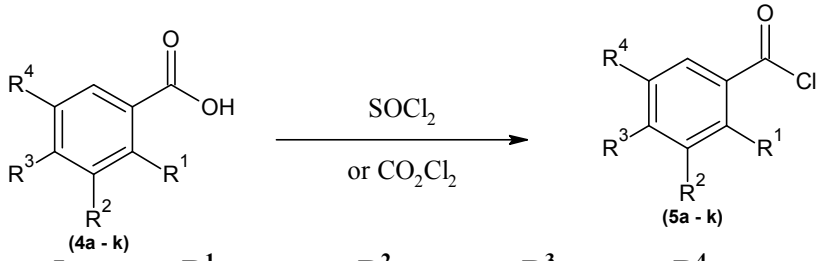


cyclopropanecarbonyl chloride
(5m)



cyclohexanecarbonyl chloride
(5n)

Some carboxylic acids (4a-e and 4i-k) were available in our laboratory and remaining can be synthesised by using standard methods.



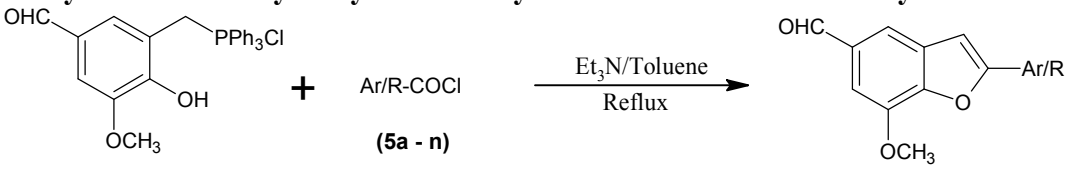
5	**R^1**	**R^2**	**R^3**	**R^4**
a	**F**	H	**F**	H
b	H	H	**SCH_3**	H
c	H	H	H	H
d	H	H	**OCH_3**	H
e	H	**OCH_3**	**OCH_3**	H
f	H	**OCH_3**	**OCH_3**	**OCH_3**
g	H	**OCH_2O**		H
h	H	**OCH_3**	**OCH_2Ph**	H
i	H	H	**CH_3**	H
j	H	**OCH_3**	H	H
k	H	H	**F**	H

The acids (4f-h) were synthesised by using standard methods. The 3,4,5-trimethoxybenzoic acid (4f) was synthesised from gallic acid. Gallic acid was methylated using dimethyl sulphate in

presence of sodium hydroxide to obtain (4f) m.p. 170-71^{0}C in 92% yield. The acid (4g) obtained by the oxidation of piperonal (using potassium permanganate) was treated with thionyl chloride in toluene under reflux conditions to obtained 3,4-methylenedioxybenzoyl chloride (5g) which was used as such for the further Wittig reaction. 3-Methoxy-4-benzyloxybenzoic acid (4h) was synthesised from vanillin. Vanillin on reaction with benzyl chloride in presence of potassium carbonate gave O-benzylvanillin [m.p. 65-66^{0}C and yield 71%]. It is on further oxidation with potassium permanganate gave acid (4h) m.p. 170-72^{0}C in 78% yield.

The benzoyl chlorides (5a-e and 5i-k) were synthesised from the corresponding benzoic acids (4a-e and 4i-k) using thionyl chloride in toluene.

2.2. Synthesis of 2-aryl/alkyl-7-methoxy-1-benzofuran-5-carbaldehyde:



Phosphonium salt **(3)** **(6a-n)**

2.2.1. Synthesis of 2-(2,4-diflurophenyl)-7-methoxy-l-benzofuran-5-carboxaldehyde (6a):

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (3.5 g, 7.5 mmol), 2,4-difluorobenzoyl chloride (**5a**) (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 2-(2,4-diflurophenyl)-7-methoxy-l-benzofuran-5-carboxaldehyde (**6a**) (1.385 g, 62%) as a faint yellow crystalline solid, m.p. 172^{0}C.

NMR (300 MHz) (DMSO-D6; δ ppm) $C_{16}H_{10}F_2O_3$ (mol. Wt. 288.245 g/mol): 3.802 (s, 3H, OCH_3), 6.866 (s, 1H); 7.192-7.179 (d, 1H); 7.320-7.261 (d, 1H); 7.682-7.721 (m, 2H); 8.124-8.067 (m, 1H), 9.96 (s, 1H).

Mass Spectra: (M+1) = 288.96, 220.95 (100%).

2.2.2. Synthesis of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (6b):

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (3.5 g, 7.5 mmol), 4-(methylsulfanyl)benzoyl chloride (**5b**) (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. 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 (**6b**) (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, 1095, 840 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.

2.2.3. Synthesis of 7-methoxy-2-phenyl-1-benzofuran-5-carbaldehyde (6c):

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (1.5 g, 0.0032 mol), benzoyl chloride (**5c**) (0.5 g, 0.0032 mol) and triethylamine (0.74 g, 0.0073 mol) in 30 ml toluene was heated under reflux for about 6 hr. The reaction mixture was cooled to room temperature and adds 20 ml cold water to it. The organic layer was separated, washed with water and dried it by using anhydrous sodium salphate. Distilled the toluene under reduced pressure and the solid obtained was recrystallized by using acetone to afford the faint yellow 7-methoxy-2-phenyl-1-benzofuran-5-carbaldehyde (**6c**) (0.40 g, 49 %), m.p. 142-43^{0}C.

FT-IR (KBr): 3035, 2942, 2844, 2721, 1691, 1592, 1475, 1342, 1218, 1139, 993, 840, 746, 719 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; δ ppm) $C_{16}H_{12}O_3$ (mol. Wt. 252.264 g/mol): 4.10 (s, 3H); 7.11 (s, 1H); 7.36-7.94 (m, 7H); 10.01 (s, 1H, -CHO).

Mass Spectra (M + 1): 253.13

2.2.4. Synthesis of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (6d):

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (3.5 g, 7.5 mmol), 4-methoxybenzoyl chloride (**5d**) (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. Separate the organic layer by separating funnel and wash it by water (2 x 50 ml) and dried over Na_2SO_4. Toluene was distilled out 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 (**6d**) (1.385 g, 62%) as a Faint Yellow crystalline solid, m.p. 170^{0}C.

FT-IR (KBr): 3010, 2977, 2935, 2709, 1693, 1612, 1598, 1513, 1228, 1133, 1024, 836 cm^{-1}.

NMR (300 MHz) (DMSO-D6; δ ppm) $C_{17}H_{14}O_4$ (mol wt: 282.290 g/mol): 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): 283.18.

2.2.5. Synthesis of 2-(3,4-dimethoxyphenyl)-7-methoxy-1-benzofuran-5-carbaldehyde (6e):

A solution of 3,4-dimethoxybenzoic acid (**4e**) (1.8 g, 0.001 mol), thionyl chloride (3.5 g, 0.029 mol) in toluene (32 ml) was refluxed for 3 hr. Toluene and excess thionyl chloride was removed under educed pressure to obtain 3,4-dimethoxybenzoyl chloride (**5e**) (1.9 g).

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (4 g, 0.0086 mol), 3,4-dimethoxybenzoyl chloride (**5e**) (1.9 g, 0.0095 mol) and triethylamine (2.0 g, 0.0198 mol) in toluene (80 ml) was heated under reflux conditions for 6 hr. The reaction mixture was cooled to room temperature and add 20 ml cold water to it. The organic layer was separated, washed with water and dried it by using anhydrous sodium salphate. Distilled the toluene under reduced pressure and the solid product formed was recrystallized from acetone : methanol (8:2) to obtained faint yellow solid 2-(3,4-dimethoxyphenyl)-7-methoxy-1-benzofuran-5-carbaldehyde (**5e**) (1.6 g, 59 %), m.p. 184-85^{0}C.

FT-IR (KBr): 3010, 2836, 2778, 1691, 1612, 1513, 1284, 1168 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; δ ppm): $C_{18}H_{16}O_2$ (mol wt: 312.3 g/mol): 3.95 (s, 3H, -OCH_3); 4.00 (s, 3H, -OCH_3); 4.10 (s, 3H, -OCH_3); 6.95 (d, J = 8.4 Hz, 1H, Ar-H); 6.99 (bs, 1H, Ar-H); 7.35

(bs, 1H, Ar-H); 7.37 (d, J = 1.8 Hz, 1H, Ar-H); 7.48 (dd, J = 8.4 & 1.8 Hz, 1H, Ar-H); 7.69 (d, J = 1.8 Hz, 1H, Ar-H); 10.04 (s, 1H, -CHO).

Mass Spectra (M + 1): 313.15

2.2.6. Synthesis of 7-methoxy-2-(3,4,5-trimethoxyphenyl)-1-benzofuran-5-carbaldehyde (6f):

A solution of 3,4,5-trimethoxybenzoic acid (**4f**) (0.8 g, 0.0037 mol) and thionyl chloride (1.35 g, 0.0113 mol) in toluene (16 ml) was heated under reflux for 3 hr. Toluene and excess thionyl chloride was distilled off under educed pressure. The residue obtained was dried in vacuum to furnish 3,4,5-trimethoxybenzoyl chloride (**5f**) (0.82 g). It is used as such for further reaction.

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (1.5 g, 0.0032 mol), 3,4,5-trimethoxybenzoyl chloride (**5f**) (0.82, 0.0032 mol) and triethylamine (0.75 g, 0.0074 mol) in toluene (30 ml) was heated under reflux for 3 hr. The reaction mixture was cooled to room temperature and water (20 ml) was added to it. The organic layer was separated, washed with water and dried by anhydrous sodium salphate. Toluene was distilled off under reduced pressure and the solid obtained was crystallized from acetone to afford the 7-methoxy-2-(3,4,5-trimethoxyphenyl)-1-benzofuran-5-carbaldehyde (**6f**) (0.65 g, 59%), yellow crystalline solid, m.p. 167-69^{0}C

FT-IR (KBr): 2942, 1691, 1614, 1594, 1504, 1332, 1251, 1128, 1010, 817, 773 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; δ ppm): $C_{19}H_{18}O_6$ (mol wt: 342.342 g/mol): 3.91 (s, 3H); 3.97 (s, 3H), 4.10 (s, 3H); 7.05 (s, 1H); 7.10 (s, 2H); 7.38 (s, 1H); 7.71 (s, 1H); 10.01 (s, 1H, CHO).

Mass Spectra (M + 1): 343.18

2.2.7. Synthesis of 2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-carbaldehyde (6g):

A solution of 3,4-methylenedioxybenzoic acid (**4g**) (1.4 g, 0.0084 mol) and thionyl chloride (3.0 g, 0.0252 mol) in toluene (28 ml) was heated under reflux for 3 hr. Toluene and excess thionyl chloride was removed under educed pressure and the residue obtained was dried in vacuum to furnish 3,4-methylenedioxybenzoyl chloride (**5g**) (1.45 g) which was used as such for further reaction.

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (3.5 g, 0.0075 mol), 3,4-methylenedioxybenzoyl chloride (**5g**) (1.45 g, 0.0078 mol) and triethylamine (1.6 g, 0.016 mol) in toluene (70 ml) was heated under reflux for 6 hr. The reaction mixture was cooled to room temperature and water (50 ml) was added to it. The organic layer was separated, washed with water (2 x 50 ml) and dried by anhydrous sodium salphate. Toluene was distilled off under reduced pressure and the solid obtained was crystallized from acetone to afford the 2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-carbaldehyde (**6g**) (1.385 g, 62%), yellow crystalline solid, m.p. 178-79^{0}C.

FT-IR (KBr): 2960, 2906, 1698, 1592, 1477, 1338, 1243, 1139, 1106, 1037, 929, 836 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; δ ppm): $C_{17}H_{12}O_5$ (mol wt: 296.274 g/mol): 4.08 (s, 3H); 6.03 (s, 2H); 6.89 (d, J = 8.1 Hz, 1H); 6.94 (s, 1H); 7.33 (d, J = 1.8 Hz, 1H); 7.35 (d, J = 1.8 Hz, 1H); 7.43 (dd, J = 1.8 & 8.1 Hz, 1H); 7.68 (d, J = 1.8 Hz, 1H); 10.01 (s, 1H, CHO).

Mass Spectra (M + 1): 297.12

2.2.8. Synthesis of 2-[4-(benzyloxy)-3-methoxyphenyl]-7-methoxy-1-benzofuran-5-carbaldehyde (6h):

A solution of 3-methoxy-4-benzyloxybenzoic acid (**4h**) (0.7 g, 0.0027 mol) and thionyl chloride (0.96 g, 0.008 mol) in toluene (14 ml) was heated under reflux for 3 hr. Toluene and excess thionyl chloride was removed under educed pressure and the residue obtained was dried in

vacuum to furnish 3-methoxy-4-benzyloxybenzoyl chloride (**5h**) (0.66 g) which was used as such for further reaction.

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (1.0 g, 0.0021 mol), 3-methoxy-4-benzyloxybenzoyl chloride (**5h**) (0.66 g, 0.0024 mol) and triethylamine (0.5 g, 0.0049 mol) in toluene (20 ml) was heated under reflux for 2 hr. The reaction mixture was cooled to room temperature and water (15 ml) was added to it. The organic layer was separated, washed with water (2 x 10 ml) and dried by anhydrous sodium salphate. Toluene was distilled off under reduced pressure and the solid obtained was crystallized from acetone to afford the 2-[4-(benzyloxy)-3-methoxyphenyl]-7-methoxy-1-benzofuran-5-carbaldehyde (**6h**) (0.48 g, 58 %), yellow crystalline solid, m.p. 141-42^{0}C.

FT-IR (KBr): 2962, 2825, 2775, 1685, 1616, 1509, 1367, 1321, 1286, 1126, 927, 754 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; δ ppm): $C_{24}H_{20}O_5$ (mol wt: 388.412 g/mol): 4.00 (s, 3H); 4.09 (s, 3H); 5.21 (s, 2H); 6.94-6.98 (m, 2H); 7.32-7.48 (m, 8H); 7.68 (bs, 1H); 9.99 (s, 1H, CHO).

Mass Spectra (M + 1): 389.13

2.2.9. Synthesis of 7-methoxy-2-(4-methylphenyl)-1-benzofuran-5-carbaldehyde $C_{17}H_{14}O_3$ (Mol. Wt. 266.291 g/mol) (6i):

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (1.5 g, 0.0032 mol), 4-methybenzoyl chloride (**5i**) (0.0032 mol) and triethylamine (0.75 g, 0.0074 mol) in toluene (30 ml) was heated under reflux for 4 hr. The reaction mixture was cooled to room temperature and add 20 ml water to it and shake well. The organic layer was separated, washed with 10 ml water and dried by anhydrous sodium salphate. Toluene was distilled off under reduced pressure and the (faint yellow) solid obtained was purified by column chromatography (using 40% ethyl acetate in pet ether as mobile phase) to afford the solid 7-methoxy-2-(4-methyphenyl)-1-benzofuran-5-carbaldehyde (**6i**) (54 %), yellow crystalline solid, m.p. 139-141^{0}C

FT-IR (KBr): 3052, 2857, 1697, 1610, 1598, 1477, 1438, 1342, 1145, 912, 721 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; δ ppm): $C_{17}H_{14}O_3$ (mol wt: 266.29 g/mol): 2.34 (s, 3H, -CH_3); 4.03 (s, 3H, -OCH_3); 7.10 (s, 1H, furan-H); 7.30 (t, 2H, Ar-H); 7.38 (s, 1H, Ar-H); 7.58 (dd, 2H, Ar-H); 7.85 (s, 1H, Ar-H); 10.00 (s, 1H, -CHO).

Mass spectra (M + 1) = 267.16

2.2.10. Synthesis of 7-methoxy-2-(3-methoxylphenyl)-1-benzofuran-5-carbaldehyde (6j):

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (1.5 g, 0.0032 mol), 3-methoxybenzoyl chloride (**5j**) (0.0032 mol) and triethylamine (0.75 g, 0.0074 mol) in toluene (30 ml) was heated under reflux for 5 hr. The completion of reaction was confirmed by TLC. The reaction mixture was cooled to room temperature and adds 20 ml water to it and shake well. The organic layer was separated, washed with 10 ml water and dried by anhydrous sodium salphate. Toluene was distilled off under reduced pressure and the (faint yellow) solid obtained was purified by column chromatography (using 35% ethyl acetate in pet ether as mobile phase) to afford the solid 7-methoxy-2-(3-methoxyphenyl)-1-benzofuran-5-carbaldehyde (**6j**) (62 %), yellow solid, m.p. 125-127 ^{0}C.

FT-IR (KBr): 2954, 1685, 1554, 1482, 1344, 1214, 1143, 846, 775, 682 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; δ ppm): $C_{17}H_{14}O_4$ (Mol. Wt. 282.290 g/mol): 3.84 (s, 3H, -OCH_3-m); 4.03 (s, 3H, OCH_3-p); 6.99 (d, J = 3Hz, 1H, Ar-H); 7.42 (dd, J = 3 & 5Hz, 1H, Ar-H); 7.38 (d, J = 3Hz, 1H, Ar-H); 7.50-7.59 (m, 3H); 7.85 (s, 1H); 10.00 (s, 1H, -CHO).

Mass Spectra (M + 1): 283.14

2.2.11. **Synthesis of 2-(4-fluorophenyl)-7-methoxy-1-benzofuran-5-carbaldehyde (6k):**
A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (1.5 g, 0.0032 mol), 4-fluorobenzoyl chloride (**5k**) (0.0032 mol) and triethylamine (0.75 g, 0.0074 mol) in toluene (30 ml) was heated under reflux for 4.5 hr. The completion of reaction was confirmed by using TLC. The reaction mixture was cooled to room temperature and adds 20 ml water to it and shake well. The organic layer was separated, washed with 10 ml water and dried by anhydrous sodium salphate. Toluene was distilled off under reduced pressure and the (faint yellow) solid obtained was purified by column chromatography (using 40% ethyl acetate in pet ether as mobile phase) to afford the solid 2-(4-fluorophenyl)-7-methoxy-1-benzofuran-5-carbaldehyde (**6k**) (57 %), yellow crystalline solid, m.p. 126-128 ^{0}C
FT-IR (KBr): 3056, 2838, 1695, 1596, 1504, 1438, 1191, 1120, 833, 721 cm^{-1}.
NMR (300 MHz) (CDCl$_3$; δ ppm): $C_{16}H_{11}FO_3$ (Mol. Wt. 270.255 g/mol): 4.02 (s, 3H, OCH_3); 7.01 (s, 1H, Ar-H); 7.21 – 7.38 (m, 3H, Ar-H); 7.58 (t, J = 8Hz, 2H, Ar-H); 7.85 (s, 1H, Ar-H); 9.99 (s, 1H, -CHO).
Mass Spectra (M + 1): 271.13
2.2.12. Synthesis of 7-methoxy-2-(4-methyl-1,3-thiazol-2-yl)-1-benzofuran-5-carbaldehyde (6l):
A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (1.5 g, 0.0032 mol), 4-methyl-1,3-thiazole-2-carbonyl chloride (**5l**) (0.0032 mol) and triethylamine (0.75 g, 0.0074 mol) in toluene (30 ml) was heated under reflux for 5 hr. The completion of reaction was confirmed by using TLC. The reaction mixture was cooled to room temperature and adds 20 ml water to it and shake well. The organic layer was separated, washed with 10 ml water and dried by anhydrous sodium salphate. Toluene was distilled off under reduced pressure and the (reddish yellow) solid obtained was purified by column chromatography (using 40% ethyl acetate in pet ether as mobile phase) to afford the solid 7-methoxy-2-(4-methyl-1,3-thiazol-2-yl)-1-benzofuran-5-carbaldehyde (**6l**) (43 %), yellow crystalline solid, m.p. 116-118 ^{0}C
FT-IR (KBr): 3070, 2852, 1691, 1616, 1594, 1481, 1434, 1340, 1141, 744 cm^{-1}.
NMR (300 MHz) (CDCl$_3$; δ ppm): $C_{14}H_{11}NO_3S$ (Mol. Wt. 273.30 g/mol): 2.24 (s, 3H, $-CH_3$); 4.00 (s, 3H, $-OCH_3$); 7.22 (s, 1H, Ar-H); 7.36 (s, 1H, Ar-H); 7.46 (s, 1H, Ar-H); 7.79 (s, 1H, Ar-H); 9.97 (s, 1H, -CHO).
Mass spectra (M + 1): 274.41
2.2.15. Synthesis of 2-cyclopropyl-7-methoxy-1-benzofuran-5-carbaldehyde (6m):
A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (1.5 g, 0.0032 mol), cyclopropyl carbonyl chloride (**5m**) (0.0032 mol) and triethylamine (0.75 g, 0.0074 mol) in toluene (30 ml) was heated under reflux for 3.5 hr. The reaction mixture was cooled to room temperature and add 20 ml water to it and shake well. The organic layer was separated, washed with 10 ml water and dried by anhydrous sodium salphate. Toluene was distilled off under reduced pressure and the yellowish red color liquid obtained, it was purified by distillation to afford the reddish yellow color liquid 2-cyclopropyl-7-methoxy-1-benzofuran-5-carbaldehyde (**6m**) (63 %), b.p. 172 ^{0}C.
FT-IR (KBr): 3070, 3002, 2923, 2852, 1685, 1617, 1594, 1344, 1141 cm^{-1}.
NMR (300 MHz) (CDCl$_3$; δ ppm): $C_{13}H_{12}O_3$ (Mol. Wt. 216.232 g/mol): 1.29 (d, J = 8Hz, 4H, $-CH_2-$); 2.16 (m, 1H, -CH-); 3.96 (s, 3H, OCH_3); 6.83 (s, 1H, Ar-H); 7.38 (d, J = 3Hz, 1H, Ar-H); 7.74 (d, J = 3Hz, 1H, Ar-H); 9.98 (s, 1H, -CHO).
Mass spectra (M + 1): 217.31

2.2.16. Synthesis of 2-cyclohexyl-7-methoxy-1-benzofuran-5-carbaldehyde (6n):
A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**3**) (1.5 g, 0.0032 mol), cyclohexyl carbonyl chloride (**5n**) (0.0032 mol) and triethylamine (0.75 g, 0.0074 mol) in toluene (30 ml) was heated under reflux for 3 hr. The reaction mixture was cooled to room temperature and add 20 ml water to it and shake well. The organic layer was separated, washed with 10 ml water and dried by anhydrous sodium salphate. Toluene was distilled off under reduced pressure and the yellowish red color liquid obtained, it was purified by distillation to afford the yellow color liquid 2-cyclohexyl-7-methoxy-1-benzofuran-5-carbaldehyde (**6n**) (63 %), b.p. 190-192 ^{0}C
FT-IR (KBr): 2933, 2856, 1693, 1592, 1542, 1481, 1438, 1340, 1141, 723, 541 cm^{-1}.
NMR (300 MHz) ($CDCl_3$; δ ppm): $C_{16}H_{18}O_3$ (Mol. Wt. 258.31 g/mol): 1.16 (m, 2H, -CH_2-); 1.36 (m, 4H, -CH_2-); 1.59 (m, 4H, -CH_2-); 1.96 (m, 1H, -CH-); 3.99 (s, 3H, -OCH_3); 6.98 (s, 1H, Ar-H); 7.34 (d, 1H, Ar-H); 7.71 (d, 1H, Ar-H); 9.96 (s, 1H, -CHO).
Mass spectra (M + 1): 259.26

RESULT AND DISCUSSION:
We have visualized the route involving intramolecular Wittig reaction for the synthesis of 2-aryl/alkyl-7-methoxybenzofuran-5-carboxaldehyde from vanillin. The ester functional group is less reactive than aldehyde or ketone functional group in Wittig carbonyl olefination. In our work, we visualizing that the phosphorane might react with ester functionality in intramolecular fashion. Vanillin (**1**) undergoes Mannich reaction forming corresponding Mannich base (**2**) by the procedure developed by Sinhababu and Borchardt. They have achieved its synthesis by treating vanillin with dimethylamine and formaldehyde in ethyl alcohol solution forming product (**2**). We have observed that, instead of ethyl alcohol, if methyl alcohol is used, the reaction is more clean and the product obtained in slightly better yield. The phosphonium salt (**3**) was synthesized in three steps. A solution of Mannich base (**2**) in acetic anhydride was reflux for about 24 hours to give the crude diacetate. The diacetate without purification was reacted with concentrated hydrochloric acid to give the brown coloured chloromethyl derivative in 99% yield. The chloromethyl derivative on reaction with triphenylphosphine in dry benzene under reflux condition provided the phosphonium salt (**3**) [m.p. 254^{0}C (decompose), yield 79%]. The phosphonium salt (**3**) showed the positive $FeCl_3$ colouration, Tollen's test (by using silver ammonia complex) and positive 2,4-DNP test.
The presence of –OH group (~ 3430 cm^{-1}) and –CHO group are confirmed by FTIR (KBr) spectra. The phosphonium salt (**3**) has been react with various acid chlorides (**5a-n**) forming corresponding 7-methoxy-5-formylbenzofuran derivatives (**6a-n**). The acid chlorides (**5a-n**) are obtained from corresponding carboxylic acid (**4a-k**) and thionyl chloride.
The presence of free aldehyde functional group can be confirmed by NMR and IR (KBr) spectra. The aldehydic carbonyl group shows strong absorption band at 1695-1685 cm^{-1} is due to C=O stretching vibrations. The absorption shifted towards lower wave number side indicate that –CHO group is attached to aromatic ring (aromatic aldehyde). The two weak bands in the region of 2720 – 2850 cm^{-1} are due to C-H stretching vibrations of CHO group. All the aldehydes (**5a-n**) shows absorption in the region 1220-1280 cm^{-1} is due to stretching vibrations of C-O-C bond. The phenyl ring (mono-substituted benzene ring) substituted at 2-position in aldehyde (**5c**) has been confirmed from its FT-IR spectra, it shows two absorption bands (746 & 719 cm^{-1}) in the region 770 – 690 cm^{-1}. The presence of 1,3-disubstituted ring in (**5j**) can be confirmed from its

FT-IR spectra. It shows strong three absorption bands at 846, 775 and 682 cm^{-1} (region 900 – 680 cm^{-1}). The presence of 1,4-disubstituted benzene ring at 2-position of benzofuran nucleus has been confirmed by =C-H bending vibration (in the region 1400-1000 cm^{-1}) & strong band in the region 860 – 800 cm^{-1}. The bending vibrations of aliphatic $–CH_2-$ and $–CH_3$ group shows absorption in the region 1480-1440 and 1370-1380 cm^{-1}. The aldehydes (**5i**), (**5l**), (**5m**) and (**5n**) are shows strong absorption bands at 1477, 1438, 1342; 1481, 1434, 1340; 1484, 1434, 1344 and 1481, 1438, 1340 cm^{-1} respectively indicates presence of aliphatic $–CH_2-$ and $–CH_3$ group.

Aldehyde	=C-H bending frequencies in cm^{-1}	Band in the region 860-800 cm^{-1}
5b	1141, 1095	840
5d	1133, 1024	836
5i	1145, 997	819
5k	1191, 1120	833

The $–CH_2-O-CH_2-$ group present in the aldehyde (5g) shows absorption at 1139 cm^{-1} due to C-O-C stretching vibrations. The hydrogen atom of the aldehyde shows singlet in its NMR spectra in the region 9.8 – 10.2 ppm indicates that aldehyde group is attached to fully substituted carbon atom i.e. carbon atom of benzene ring. The furan-H shows singlet in the region 6.7 – 7.22 ppm which is depend on the nature of group attached at 2-position. The final products formed have been also confirmed from its mass spectra. These results indicates that, reaction of (**3)** with acid chloride (**5a-n**) in presence of triethylamine generated *in situ* intermediate compound (ester of phosphonium salt) which is further reacts with triethylamine forming 2-alkyl/aryl-7-methoxy-5-formylbenzofuran derivatives (**6a-n**).

The heteroatom such as nitrogen (reaction with ferrous sulphate) (**5l**), sulphur (sodium nitroprusside test) (**5l**), halogen (silver nitrate test, in case of fluorine use zirconium-alizarin test) (**5a, 5k**) present in the aldehyde has been confirmed by Lassaigne's Test (sodium fusion test). In some compounds both nitrogen sulphur is present which are detected by $FeCl_3$ test (gives blood red colour) (**5l**).

2-Alkyl/aryl-5-formylbenzofurans (**6a-n**) are synthesized by intramolecular Wittig reaction in good yield. It could be used for the synthesis of several natural and synthetic 2-arylbenzofuran derivatives. e.g synthesis of compounds machicendiol and coumarines has been reported in the literature. In general, these formyl derivatives of the benzofurans are used for the synthesis of various 2-aryl/alkyl benzofuran compounds.

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