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SYNTHESIS OF SECONDARY AMINES IN ONE STEP FROM 7-METHOXY-2-[4-(METHOXY)PHENYL)-1-BENZOFURAN-5-CARBOXALDEHYDE BY REDUCTIVE AMINATION

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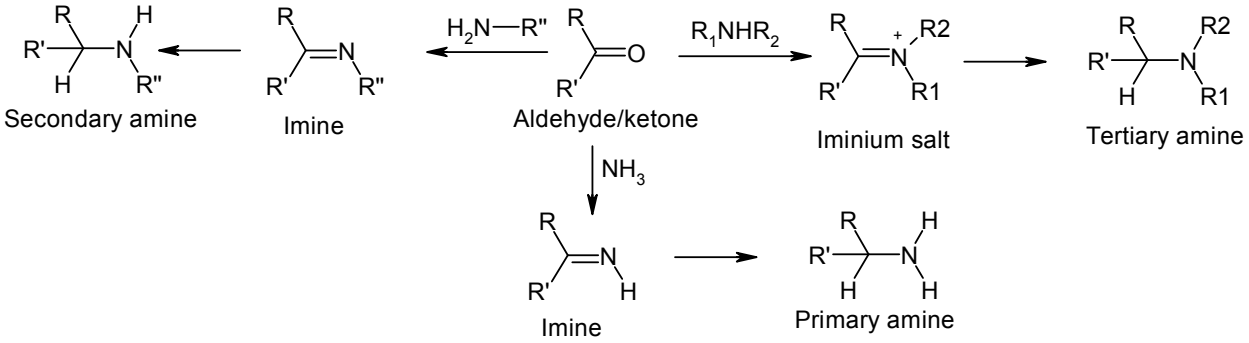
Abstract: Vanillin undergoes sequence of reaction forming phosphonium salt through dimethyaminomethyl derivative (Mannich reaction). The synthesis of phosphonium salt can be achieved by sequence of three steps. The 7-methoxy-2-[4-(methoxy)phenyl)-l-benzofuran-5-carboxaldehyde (3) was subjected to reductive amination with series of aliphatic and aromatic amines (4a-l) forming corresponding secondary amines or anilines (5a-l) which were purified by column chromatography and characterized by NMR and Mass spectroscopy.

Key Words: Benzofuran, Reductive amination, Amines, Mannich reaction, Vanillin.

1. Introduction:

The reaction of aldehydes or ketones with ammonia or primary amine or secondary amine in presence of reducing agent to gives primary or secondary or tertiary amines is known as reductive amination of the carbonyl compound or reductive alkylation of amines.



Heterocyclic compounds plays very important role in the biological system. Many heterocyclic compounds are of natural origin with useful medicinal properties have served as lead compound in the designing of synthetic drugs. Heterocyclic compounds[I,II] bearing benzofuran moieties constitute the structure of number of pharmacological and biologically active interesting

compounds. 7-Methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde was synthesized by known literature method[III]. The aldehyde is treated with various aliphatic and aromatic amines in presence of reducing agent forming corresponding amine.

The reducing agents utilizes hydride reducing agents particularly sodium cyanoborohydride ($NaBH_3CN$) for reduction[IV,V]. 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[VI]. At pH = 3-4, it reduces ketones, but this become slowly at higher pH. At pH 6-8, the more basic imines are protonated preferentially and reduce faster than aldehydes and ketones[VI]. The other hydride reducing reagents reported for the reductive amination are- boron-pyridine (BH_3-Py)[VII], $Ti(O^iPr)_4/NaBH_3CN$[VIII], borohydride exchange resin[IX], Zn/AcOH[X], $NaBH_4/Mg(ClO_4)_2$[XI], $Zn(BH_4)_2/ZnCl_2$[XII], etc. Some reports of electrochemical reductive amination have been also reported[XIII]. After surveying many commercially available hydride reducing reagents, sodium triacetoxyborohydride [$NaBH(OAc)_3$][XIV] is the mild reducing reagent and exhibits remarkable selectivity as a reducing agent.

2. Experimental Work:

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

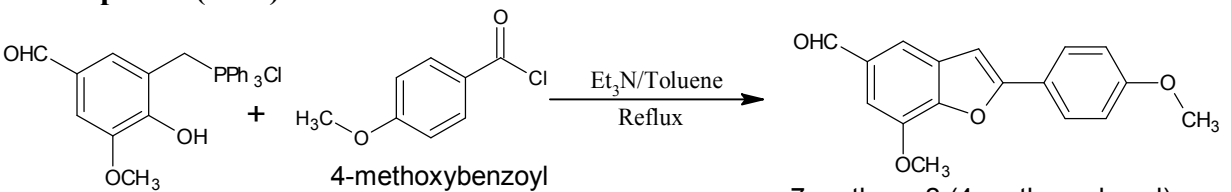
A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (**1**) (3.5 g, 7.5 mmol), 4-methoxybenzoyl chloride (**2**) (1.34 g, 7.8 mmol) and triethylamine (1.6 g, 16 mmol), in toluene (70 ml) was heated under reflux for 6 hrs. The reaction mixture was cooled to room temperature 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 (**3**) (1.385 g, 62%) as a white crystalline solid, m.p. 170^0C.

Molecular formula: $C_{17}H_{14}O_4$**; Color:** Faint Yellow solid**; Yield:** 62%**; m.p.:** 170^0C

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

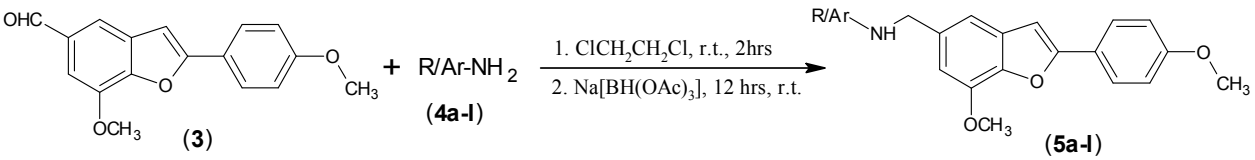
NMR (300 MHz) (DMSO-D6; ð ppm) $C_{17}H_{14}O_4$ (mol wt: 282.290 g/mol): 10.01 (s, 1H, -CHO), 7.86 – 7.891 (m, 3H, 3 Aromatic protons), 7.42 (dd, 2H, Aromatic protons), 7.09 (dd, 2H, Aromatic protons), 4.046 (s, 3H, $-OCH_3$), 3.831 (s, 3H, $-OCH_3$).

Mass Spectra (M+1): 283.18.



2.2. Synthesis of secondary amines (5a-l) from 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (3):

The aldehyde (**3**) was treated with various aliphatic and aromatic amines (**4a-l**) in dichloroethane in presence of reducing agent at room temperature forming series of secondary amines (**5a-l**) is the named reaction called as reductive amination.



Amine	Product	Amine	Product
3-chloroaniline (4a)	5a	3-fluoroaniline (4b)	5b
4-chloro-3-trifluoromethylaniline (4c)	5c	2,4,5-trichloroaniline (4d)	5d
3-trifluoromethylaniline (4e)	5e	4-bromo-2-fluoroaniline (4f)	5f
Cyclopentanamine (4g)	5g	(1R)-1-phenylethanamine (4h)	5h
2-methoxyethanol (4i)	5i	morpholin-4-amine (4j)	5j
1-methylpiperidin-4-amine (4k)	5k	2-(morpholin-4-yl)ethanamine (4l)	5l

2.2.1. 3-Chloro-*N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl} aniline (5a):

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl)-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and 3-fluoroaniline (**4a**) (52 ml, 0.57 mmol) in ethylene dichloride (5 ml), add catalytic amount of acetic acid. Stirred the reaction for 2 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 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 150 mg 3-chloro-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}aniline (**5a**) having yield 83% and m.p. 165 ^{0}C.

Molecular formula: $C_{23}H_{20}NO_4Cl$; **Color:** buff white solid**; Yield:** 83%**; m.p.:** 165 ^{0}C

NMR (300 MHz) ($CDCl_3$; ð ppm): 7.82-7.798 (t, 2H), 7.146-7.068 (m, 2H), 6.981-6.952 (t, 2H), 6.836 (s, 1H), 6.783 (s, 1H), 6.441-6.343 (m, 3H), 6.30 (bs, NH), 4.355 (s, 2H, -CH_2-N), 4.039 (s, 3H), 3.860 (s, 3H).

Mass Spectra: 392 (M^+); 394 (M+2).

2.2.2. 3-Fluoro-*N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl} aniline (5b):

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl)-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and 3-fluoroaniline (**4b**) (61 □l, 0.57 mmol) in ethylene dichloride (5 ml), add catalytic amount of acetic acid. Stirred the reaction mixture for 2 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 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 150 mg 3-fluoro-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}aniline (**5b**) having yield 86% and m.p 127 – 128 ^{0}C.

Molecular formula: $C_{23}H_{20}NO_4F$**; Color:** Buff white solid**; Yield:** 86%**; m.p.:** 127 – 128 ^{0}C
FT-IR (KBr): 3345, 1615, 1582, 1356, 1243, 834 cm^{-1}.
NMR (300 MHz) ($CDCl_3$; ð ppm): 7.82 (s, 1H), 7.79 (s, 1H), 7.26 (s, 1H), 7.13 (m, 1H), 6.97 (dd, 2H), 6.83 (s, 1H), 6.76 (m, 1H), 6.65 (dd, 2H), 6.51 (m, 1H), 4.35 (s, 2H, -CH_2-N), 4.146 (bs, NH), 4.039 (s, 3H), 3.860 (s, 3H).
Mass Spectra: (M + 3) = 395.47, (M + 2) = 394.15, M^+ = 392.21.

2.2.3. 4-Chloro-3-trifluoromethyl-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}aniline (5c):

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and 4-chloro-3-trifluoromethylaniline (**4c**) (105.57 mg, 0.54 mmol) in ethylene dichloride (7 ml), add catalytic amount of acetic acid. Stirred the reaction for 2 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 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 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 150 mg 4-Fluoro-3-trifluoromethyl-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl} aniline (**5c**) having yield 73% and m.p. 145 ^{0}C.
Molecular formula: $C_{24}H_{19}NClO_3F_3$**; Color:** Buff white solid**; Yield:** 73%**; m.p.:** 145 ^{0}C
FT-IR (KBr): 3436, 2931, 1627, 1513, 1315, 1257, 848 cm^{-1}.
NMR (300 MHz) ($CDCl_3$; ð ppm): 7.86 (d, 1H, Ar-H); 7.83 (s, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.68 (s, 1H, Ar-H); 7.56 (d, 1H, Ar-H); 7.28 (s, 1H, Ar-H), 6.97 (dd, 2H, Ar-H), 6.76 (d, 2H, Ar-H), 6.28 (bs, 1H, NH-proton), 4.38 (s, 2H, -CH_2-N), 4.040 (s, 3H, OCH_3), 3.860 (s, 3H, OCH_3).
Mass Spectra: 446 (molecular ion peak).

2.2.4. 2,4,5-Trichloro-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl} aniline (5d):

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and 2,4,5-trichloroaniline (**4d**) (105.84 mg, 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 2,4,5-Trichloro-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}aniline (**5d**) having yield 72% and m.p. 223 ^{0}C
Molecular formula: $C_{23}H_{18}NO_3Cl_3$**; Color:** White solid**; Yield:** 72%**; m.p.:** 223 ^{0}C
FT-IR (KBr): 3370, 2931, 1612, 1515, 1328, 1228, 836 cm^{-1}.
NMR (300 MHz) ($CDCl_3$; ð ppm): 8.12 (s, 1H, Ar-H); 7.90 (s, 1H, Ar-H); 7.84 (s, 1H, Ar-H), 7.81 (s, 1H, Ar-H); 7.32 (s, 1H, Ar-H), 6.99 (dd, 2H, Ar-H), 6.78 (d, 2H, Ar-H), 6.34 (bs, 1H, NH-proton), 4.40 (s, 2H, -CH_2-N), 4.045 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3).
Mass Spectra (m/z): 462 (M^+), 463, 464.

2.2.5. 3-Trifluoromethyl-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl} aniline (5e):

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and 3-trifluoromethylaniline (**4e**) (86.94 mg, 0.54 mmol) in ethylene dichloride (7 ml), add catalytic amount of acetic acid. Stirred the reaction for 2.0 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 (25 ml 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 3-trifluoromethyl-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}aniline (**5e**) having yield 76% and m.p. 145 ^{0}C.

Molecular formula: $C_{24}H_{20}NO_3F_3$**; Color:** Faint Yellow solid**; Yield:** 76%**; m.p.:** 145 ^{0}C

FT-IR (KBr): 3380, 2938, 1629, 1590, 1332, 1274, 854 cm^{-1}.

NMR (300 MHz) (DMSO-D6; ð ppm): 3.95 (s, 3H, OCH_3); 4.055 (m, 7H, OCH_3, NH & N-CH_2); 7.10 (t, J = 6Hz, 2H, 2 Ar-H); 7.30 (d, 1H, J = 3Hz, Ar-H); 7.40 (d, J = 6Hz, 1H, Ar-H); 7.46 (t, J = 6Hz, 2H, 2 Ar-H); 7.53 (d, 1H, J = 3Hz, Ar-H); 7.63 (d, J = 3Hz, 1H, Ar-H); 7.78 (dd, J = 6Hz & J = 3Hz, 1H, Ar-H); 8.72 (s, 1H).

Mass Spectra: 428.62 (M+1).

2.2.6. 4-Bromo-2-Fluoro-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl} aniline (5f):

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and 4-bromo-2-fluoroaniline (**4f**) (102.3 mg, 0.54 mmol) in ethylene dichloride (7 ml), add catalytic amount of acetic acid. Stirred the reaction for 3.5 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 4-Bromo-2-Fluoro-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl} aniline (**5f**) having yield 74% and m.p. 190 ^{0}C.

Molecular formula: $C_{23}H_{19}NO_3BrF$**; Color:** Faint Yellow solid**; Yield:** 74%**; m.p.:** 190 ^{0}C

FT-IR (KBr): 3368, 2932, 1610, 1594, 1328, 1228, 840 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; ð ppm): 7.980 (d, 1H, Ar-H); 7.950 (s, 1H, Ar-H); 7.844 (d, 1H, Ar-H), 7.802 (s, 1H, Ar-H), 7.778 (s, 1H, Ar-H); 7.282 (s, 1H, Ar-H), 6.945 (dd, 2H, Ar-H), 6.758 (d, 2H, Ar-H), 6.152 (bs, 1H, NH-proton), 4.448 (s, 2H, -CH_2-N), 4.045 (s, 3H, OCH_3), 3.861 (s, 3H, OCH_3).

Mass Spectra: 456 (M^+).

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

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and cyclopentamine (**4g**) (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 (**5g**) having yield 74 % and m.p. 120 – 121 ^{0}C.

Molecular formula: $C_{22}H_{25}NO_3$**; Color:** Faint Yellow solid**; Yield:** 74 %**; m.p.:** 120 – 121 ^{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) ($CDCl_3$; ð 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.

2.2.8. Synthesis of (1*R*)-1-phenyl-*N*-[(7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl)methyl]ethanamine (5h):

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and (1R)-1-phenylethanamine (**4h**) (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 (1*R*)-1-phenyl-*N*-[(7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl)methyl]ethanamine (**5h**) having yield 76 % and m.p. 105 - 106 ^{0}C.

Molecular formula: $C_{22}H_{25}NO_3$**; Color:** White solid**; Yield:** 76 %**; m.p.:** 105 - 106 ^{0}C
FT-IR (KBr): 3343, 3027, 2838, 1616, 1602, 1509, 1305, 1249, 1147, 829, 698 cm^{-1}.
NMR (300 MHz) ($CDCl_3$; ð ppm): 1.328 (d, 3H, C-CH_3); 3.625 (q, 1H, N-CH); 3.818 (bs, 5H, N-CH_2 & OCH_3); 3.950 (s, 3H, OCH_3); 3.019 (bs, 1H, NH); 6.874 (s, 1H, Furan-H); 7.060 (dd, 2H, J = 9Hz); 7.205 (s, 1H); 7.254 (s, 1H); 7.329 – 7.389 (m, 5H); 7.807 - 7.836 (dd, 2H, J = 9Hz).
Mass Spectra (m/z): 256, 330, 332, 386 (base ion peak), 388 (M+1), 389 (M+2).

2.2.9. Synthesis of 2-methoxy-*N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}ethanamine (5i):

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and 2-methoxyethanamine (**4i**) (0.54 mmol) in ethylene dichloride (7 ml), add catalytic amount of acetic acid. Stirred the reaction for 90 minutes 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 20% methanol in chloroform) obtain 2-methoxy-*N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}ethanamine (**5i**) having yield 84 % and m.p. 106-108 ^{0}C.

Molecular formula: $C_{20}H_{23}NO_4$**; Color:** Dark Red solid**; Yield:** 84 %**; m.p.:** 106-108 ^{0}C

FT-IR (KBr): 3247, 2937, 1616, 1596, 1401, 1251, 1110, 1041, 912, 829, 800, 620 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; ð ppm): 2.796 (t, 2H, J = 6Hz); 3.257 (s, 2H, N-CH_2); 3.460 (t, 2H, J = 6Hz); 3.817 (s, 3H, OCH_3); 3.964 (s, 3H, OCH_3); 6.019 (s, 1H, -NH-); 6.986 (s, 1H, Furan-H); 7.048 – 7.077 (dd, 2H, J = 9Hz); 7.178 (s, 1H); 7.244 (s, 1H); 7.813 – 7.842 (dd, 2H, J = 9Hz).

Mass Spectra (m/z): 267, 268, 340 (M-1), 342 (M+1), 343 (M+2).

2.2.10. Synthesis of *N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}morpholin-4-amine (5j)

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and morpholin-4-amine (**4j**) (0.54 mmol) in ethylene dichloride (7 ml), add catalytic amount of acetic acid. Stirred the reaction for 85 minutes 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 20% methanol in chloroform) obtain *N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}morpholin-4-amine (**5j**) having yield 78 % and m.p. 86 – 88 ^{0}C.

Molecular formula: $C_{21}H_{24}N_2O_4$**; Color:** Faint Yellow solid**; Yield:** 78 %**; m.p.:** 86 – 88 ^{0}C.

FT-IR (KBr): 3471, 2969, 2844, 1614, 1579, 1506, 1365, 1253, 1151, 1118, 1008, 914, 840, 713 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; ð ppm): 3.101 – 3.114 (m, 4H, N-CH_2); 3.347 (s, 2H, N-CH_2); 3.776 (m, 6H); 3.818 (s, 3H, OCH_3); 3.976 (s, 3H, OCH_3); 7.053 – 7.082 (dd, 2H, J = 9Hz); 7.210 (s, 1H); 7.267 (s, 1H); 7.340 (s, 1H, Furan-H); 7.781 (s, 1H, NH); 7.815 – 7.844 (dd, 2H, J = 9Hz).

Mass Spectra (m/z): 282, 367, 368, 383 (M+1).

2.2.11. Synthesis of 1-methyl-*N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}piperidin-4-amine (5k):

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and 1-methylpiperidin-4-amine (**4k**) (0.54 mmol) in ethylene dichloride (7 ml), add catalytic amount of acetic acid. Stirred the reaction for 90 minutes 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 20% methanol in chloroform) obtain 1-methyl-*N*-

{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}piperidin-4-amine (5k) having yield 74 % and m.p. 95 – 97 ^{0}C.

Molecular formula: $C_{23}H_{28}N_2O_3$; **Color:** Faint Yellow solid**; Yield:** 74 %**; m.p.:** 95 – 97 ^{0}C.

FT-IR (KBr): 3411, 2935, 1610, 1156, 1503, 1440, 1305, 1257, 1176, 1151, 1120, 1024, 912, 838, 710 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; ð ppm): 2.510 (m, 4H, -CH_2-C); 2.871 – 2.995 (m, 8H, N-CH_2, -N-CH_3, -N-CH-); 3.451 (s, 2H, NH-CH_2-); 3.820 (s, 3H, OCH_3); 3.954 (s, 3H, OCH_3); 6.019 (s, 1H, -NH-); 6.951 (s, 1H, Furan-H); 7.072 – 7.041 (dd, 2H, J = 9Hz); 7.140 (s, 1H); 7.224 (s, 1H); 7.841 – 7.812 (dd, 2H, J = 9Hz).

Mass Spectra (m/z): 267, 301, 315, 381 (M+1), 382 (M+2).

2.2.12. Synthesis of 2-(morpholin-4-yl)-*N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}ethanamine (5l)

To a stirred solution of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**3**) (130 mg, 0.48 mmol) and 2-(morpholin-4-yl)ethanamine (**4l**) (0.54 mmol) in ethylene dichloride (7 ml), add catalytic amount of acetic acid. Stirred the reaction for 85 minutes 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 20% methanol in chloroform) obtain 2-(morpholin-4-yl)-*N*-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}ethanamine **(5l)** having yield 76 % and m.p. 88 – 90 ^{0}C.

Molecular formula: $C_{23}H_{28}N_2O_4$; **Color:** Faint Yellow solid**; Yield:** 76 %**; m.p.:** 88 – 90 ^{0}C.

FT-IR (KBr): 3421, 2938, 2842, 1612, 1554, 1509, 1442, 1305, 1253, 1149, 1112, 1024, 912, 744, 615 cm^{-1}.

NMR (300 MHz) ($CDCl_3$; ð ppm): 2.420 (t, 2H, J = 6Hz, N-CH_2); 2.326 (m, 4H, N-CH_2); 2.648 (t, 2H, J = 6Hz; N-CH_2); 3.550 (m, 6H); 3.815 (s, 3H, OCH_3); 3.953 (s, 3H, OCH_3); 6.190 (s, 1H, NH); 6.949 (s, 1H, Furan-H); 7.044 – 7.074 (dd, 2H, J = 9Hz); 7.139 (s, 1H); 7.223 (s, 1H); 7.810 – 7.838 (dd, 2H, J = 9Hz).

Mass Spectra (m/z): 318, 346, 397 (M+1), 398 (M+2).

3. Result and Discussion:

7-Methoxy-2-[4-methoxyphenyl]-1-benzofuran-5-carbaldehyde was treated with substituted aromatic primary amines (anilines) 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 dissolve water, osmosis principle). The excess solvent was evaporated under reduced pressure forming solid product which was characterized by FT-IR, NMR and mass spectra & from the physical constant like m.p. The melting points of all Schiff bases and their starting compounds are recorded by using Labtronics Digital Melting point apparatus. 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 single peak in the region of 3200-3450 cm^{-1} observe in the FT-IR spectra of due to N-H stretching frequency of secondary amine indicate the formation of product. The singlet at the region of 5.5 - 3.5 of two protons indicates the presence of Ar–**CH_2**-NH protons in NMR spectra is also confirming the formation of reductive amination product. The value of chemical shift varies depending on the nature of aliphatic or aromatic group attached to nitrogen in amine or aniline.

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