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Domino synthesis of 2-arylbenzo[*b*]furans by copper(II)-catalyzed coupling of *o*-iodophenols and aryl acetylenes

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ABSTRACT

A wide range of 2-arylbenzo[*b*]furans are synthesized through domino intermolecular $C_{(aryl)}$–$C_{(alkynyl)}$ bond formation followed by intramolecular $C_{(alkynyl)}$–*O* bond forming cyclization via copper(II)-catalyzed coupling of *o*-iodophenols and aryl terminal acetylenes. This method requires neither expensive palladium catalyst nor oxophilic phosphine ligands, can tolerate different functional groups. The methodology is successfully utilized in formal synthesis of β-amyloid aggregation inhibitor 5-chloro-3-[4-(3-diethylaminopropoxy)benzoyl]-2-(4-methoxyphenyl) benzofuran.

1. Introduction

Numerous synthetically challenging and medicinally important chemicals contain benzo[*b*]furan moiety as structural units.[1] Some of the properties of pharmaceutically active molecules, which contains benzo[*b*]furans are antitumor properties,[2] inhibition of protein phosphatase 1B,[3] 5-HT_2 and 5-HT_3 antagonist activity,[4] inhibition of 5-lipoxygenase (5-LO),[4b] and antifungal properties.[5] Therefore these type of compounds can be used for treatment of cancer, cardiovascular disease, type-2 diabetes, migraines, dementia and anxiety.[2–5] Traditional synthetic methods are often multistep reactions such as dehydrative cyclization of α-(phenoxy)alkyl ketones,[6] cyclofragmentation of oxiranes,[7] acidic dehydration of *o*-hydroxybenzyl ketones,[8] base mediated decarboxylation of *o*-acylphenoxyacetic acids and esters[9] and reaction of phenols with α-acylsulfoxides.[10] However, these multi-step traditional methods suffered with limited substrate scope and do not tolerate several functional groups. Palladium catalyzed benzo[*b*]furan formation from the corresponding *o*-ethynylphenol[11] or *o*-iodophenols[12] and aryl terminal acetylenes used to be the method of choice. But the high costs of palladium salts, high oxophillicity associated with phosphine ligands, and tedious multistep processes involved in the synthesis of these ligands have made to look for alternative method particularly for large scale reactions.

Easily available metal salts of copper[13–17] or iron[18] will be the ideal replacement for expensive palladium. Particularly, copper-catalyzed domino[19] intermolecular Sonogashira coupling between *o*-iodophenols and aryl acetylenes followed by 5-*endo*-*dig* cyclization is the alternative for palladium catalyzed benzo[*b*]furan synthesis, which is not much explored in literature. The pioneering work by Castro[14a] using stoichiometric quantities of copper acetylide followed by Owen[14b] using 60 mol % Cu_2O in pyridine solvent made significant progress for copper catalyzed benzo[*b*]furan synthesis. Recently, CuI-PPh_3 catalyst developed by Miura[15] and CuI-DABCO by Heng Li[16a] were also shown to catalyze the formation of benzo[*b*]furans from *o*-iodophenols and aryl terminal acetylenes. Venkataraman et al. demonstrated that $CuNO_3$ along with PPh_3 and 1,10-phenanthroline successfully used as efficient catalyst for benzo[*b*]furan synthesis.[17] However, these advances in the field of copper complex catalyzed benzo[*b*]furan synthesis is not sufficient as most of the catalysts still require harsh reaction conditions such as high temperatures (≥120 °C),[14–16] the requirement of stoichiometric quantities of copper catalysts,[14a] poor substrate scope,[14–16] still need of oxophilic phosphine ligands[15,17] and low to moderate yields[14b,15] have generally limited the utility of copper catalyst.

As part of our ongoing research toward copper catalyzed oxidation chemistry,[20] very recently we reported copper complex catalyzed arylation of alcohols, phenols, indoles, thiols, and terminal alkynes through $C_{(aryl)}$–*O* bond formation, $C_{(aryl)}$–*N* bond formation (N-arylation of indoles), $C_{(aryl)}$–*S* bond formation, $C_{(aryl)}$–*C* bond formation and their applications in heterocycle synthesis.[21] Thus, it was a natural extension for us to investigate the BINAM-copper

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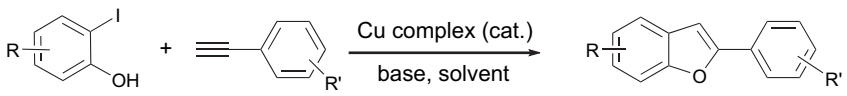
catalyzed domino Sonogashira coupling followed by 5-*endo-dig* cyclization from coupling between *o*-iodophenols and aryl acetylenes to synthesize benzo[*b*]furans (Scheme 1).



Scheme 1.

2. Results and discussion

In preliminary studies, we used 20 mol % of *N*,*N*′-dibenzyl-1,1′-binaphthyl-2,2′-diamine **L1** (dibenzyl-BINAM) (Fig. 1) as ligand with 20 mol % of $Cu(OTf)_2$ for the coupling of *o*-iodophenol with phenyl acetylene in DMSO at 110 °C. After 36 h the coupling reaction provided just 5% isolated yield with 21:79 mixture of required 2-phenylbenzo[*b*]furan **3** through domino Sonogashira coupling followed by 5-*endo-dig* cyclization and 1,3-diyne **4** through oxidative homo coupling of phenyl acetylene (Table 1, entry 1). When the solvent DMSO was replaced by DMF, the yield was increased to 13% yield with 28:72 mixture of 2-phenylbenzo[*b*]furan **3** and 1,3-diyne **4** (entry 2). Then the coupling reaction were carried out in acetonitrile, THF, and 1,4-dioxane solvents and the isolated yield increased to 41–55% with gradually increasing the required 2-phenylbenzo[*b*]furans **3** up to 91:09 (entries 3–5). Surprisingly, when the reaction was carried out in less polar solvent such as toluene, the reaction took only 32 h for completion and yielded 90% isolated yield in favor of 98:02 of required phenylbenzo[*b*]furan **3** (entry 6).

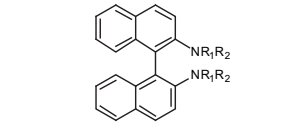
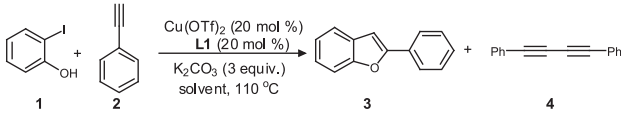


Figure 1. BINAM based ligands for copper catalyzed 2-arylbenzo[*b*]furan synthesis.

Table 1
Effect of the solvents



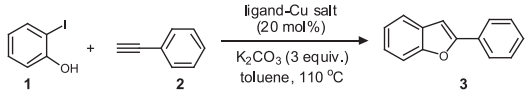
Entry	Solvent	Time (h)	Yield[a] (%)	**3**:**4**[b]
1	DMSO	36	05	21:79
2	DMF	36	13	28:72
3	Acetonitrile	56	55	62:38[c]
4	THF	64	41	70:30[c]
5	1,4-Dioxane	55	64	91:09[c]
6	Toluene	**32**	**90**	**98:02**

[a] Yield of **3**′.
[b] Determined by GC analysis using hp5 regular column (flowrate: $H_2$80 ml/m, air 250 ml/m, oven temperature: 60–250 °C).
[c] Reaction was carried out in pressure tube.

It is very clear that polar solvents such as DMSO and DMF provide poor yield and oxidative homo coupling product as major product. When comparatively moderate polar solvents such as acetonitrile, THF, and 1,4-dioxane are used, the isolated yield increased gradually and yielded required cyclized product **3** as major product. In less polar solvent like toluene, it provided highest isolated yield with required cyclized product **3** as almost single product. So it is clear that the oxidative homo coupling product **4** is favored in polar solvents, such as DMSO, DMF, and expected cyclization product **3** through domino Sonogashira coupling followed by 5-*endo-dig* cyclization favored in non-polar solvent such as toluene. Similarly the yield also increased by decreasing the polarity of the solvent.

The reaction was screened with several BINAM based ligands, copper salts, bases and different ratio of catalyst to increase the efficiency of the coupling reactions and the results are summarized in Table 2. Replacing ligand **L1** by **L2**, **L3**, and **L4** in toluene took more time for completion and the isolated yield decreased to 52%, 47%, and 41%, respectively (Table 2, entries 2–4). Although several copper salts catalyzed the reaction, $Cu(OTf)_2$ turned out to be the copper salt of choice in view of isolated yield (entry 1). When the reaction was carried out without any ligand, it provided only 35% yield for the cyclized product **3** (entry 10). K_2CO_3 as base gave the best yields of product in comparison with Cs_2CO_3 (entry 1 vs entry11). Then the reaction was carried out with different ratios of **L1** and $Cu(OTf)_2$, and it was found that 20 mol % of ligand **L1**-copper combination was the most effective catalytic system (entry 1 vs entries 12–14).

Table 2
Effect of Cu salts, bases and different ratio of catalyst



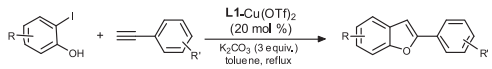
Entry	Ligands	Cu salts	Time (h)	Yield[a] (%)
1	**L1**	$Cu(OTf)_2$	32	90
2	**L2**	$Cu(OTf)_2$	48	52
3	**L3**	$Cu(OTf)_2$	52	47
4	**L4**	$Cu(OTf)_2$	52	41
5	**L1**	CuI	30	78
6	**L1**	$CuSO_4$	52	76
7	**L1**	$Cu(OAc)_2.H_2O$	53	74
8	**L1**	$CuCl_2$	49	76
9	**L1**	CuBr	50	68
10	–	$Cu(OTf)_2$	52	35
11	**L1**	$Cu(OTf)_2$	50	62[b]
12	**L1**	$Cu(OTf)_2$	66	52[c]
13	**L1**	$Cu(OTf)_2$	68	74[d]
14	**L1**	$Cu(OTf)_2$	69	56[e]

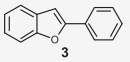
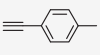
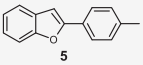
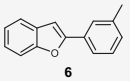
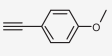
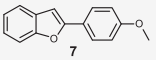
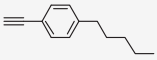
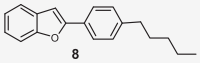
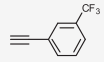
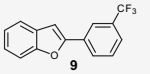
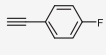
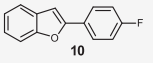
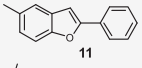
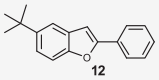
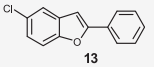
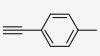
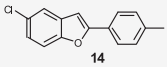
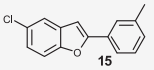
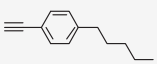
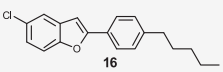
[a] Isolated yield.
[b] Cs_2CO_3 is used as base.
[c] Ratio of $Cu(OTf)_2$ and **L1** is 10:20 mol %.
[d] Ratio of $Cu(OTf)_2$ and **L1** is 10:10 mol %.
[e] Ratio of $Cu(OTf)_2$ and **L1** is 5:10 mol %.

Using the above mentioned optimized conditions, we initiated our investigations into the scope of the **L1**-$Cu(OTf)_2$ complex catalyzed domino Sonogashira coupling followed by 5-*endo-dig* cyclization for the synthesis of 2-aryl substituted benzo[*b*]furans and the results are summarized in Table 3. Various *o*-iodophenols reacted with several kinds of terminal alkynes to give the corresponding 2-aryl substituted benzo[*b*]furans under mild reaction conditions. We found that *o*-iodophenols containing electron-releasing groups (entries 8 and 9) as well as electron-withdrawing groups (entries 10–13) reacted with terminal aryl alkynes to give corresponding benzo[*b*]furans. The

o-iodophenols containing electron-withdrawing groups provided comparatively better yields for benzofurans than *o*-iodophenols containing electron-releasing groups (entries 8 and 9 vs 10–13). Similarly, terminal alkynes containing electron-releasing groups (entries 2–5) as well as electron-withdrawing groups (entries 6 and 7) reacted with *o*-iodophenols to give corresponding benzofurans. However, the terminal alkynes containing electron-releasing groups yielded comparatively better yields for benzofurans than alkynes containing electron-withdrawing group (entries 2–5 vs 6 and 7). Alkyl acetylene such as 2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran failed to provide expected 2-alkyl substituted benzofuran.

Table 3
Coupling of *o*-iodophenols with terminal aryl alkynes catalyzed by **L1**-Cu(OTf)$_2$ complex



Entry	Iodophenols	Aryl acetylenes	Products	Time (h)	Yield[a] (%)
1			 **3**	32	90
2			 **5**	39	83
3			 **6**	49	77
4			 **7**	22	80
5			 **8**	39	82
6			 **9**	24	60
7			 **10**	38	48
8			 **11**	36	60
9			 **12**	30	48
10			 **13**	36	70
11			 **14**	28	91
12			 **15**	28	90
13			 **16**	26	87

[a] Isolated yield.

2.1. Formal synthesis of β-amyloid aggregation inhibitor

After successful completion of a wide range of 2-arylbenzo[*b*]furan synthesis in the presence of **L1**-Cu(OTf)$_2$, we successfully applied the same protocol for formal synthesis of a potent β-amyloid aggregation inhibitor[22] 5-chloro-3-[4-(3-diethyl aminopropoxy)benzoyl]-2-(4-methoxyphenyl)benzofuran **22** where 2-arylbenzo[*b*]furan formation is the key step (Scheme 2). Commercially available *p*-chlorophenol was iodinated by NaOCl/NaI and NaOH in methanol to give 70% of product 4-chloro-2-iodophenol **17**, which was used as starting material to couple with *p*-methoxyphenyl acetylene **18** in the presence of catalytic amount of **L1**-Cu(OTf)$_2$ complex to give 5-chloro-2-(4-methoxyphenyl)benzofuran **19** with 80% isolated yield. Acylation of product **19** with acid chloride **20** in the presence of $SnCl_4$ gave 56% of acylated product **21**. Replacement of bromo group by diethylamine will provide the target molecule β-amyloid aggregation inhibitor **22**.[23]

Scheme 2. Formal synthesis of β-amyloid aggregation inhibitor **22** using L1-CuI catalyzed 2-arylbenzo[*b*]furan formation is the key step.

3. Conclusion

In summary, we have described an efficient, experimentally simple, and economically attractive copper catalyzed synthesis of a wide range of 2-arylbenzo[*b*]furans through domino intermolecular $C_{(aryl)}$–$C_{(alkynyl)}$ bond formation followed by intramolecular $C_{(alkynyl)}$–*O* bond formation from coupling of *o*-iodophenols with aryl acetylenes. *o*-Iodophenols containing electron-withdrawing groups provided comparatively better yields for benzofurans than *o*-iodophenols containing electron-releasing groups. Similarly, the aryl terminal alkynes containing electron-releasing groups yielded comparatively better yields for benzo[*b*]furans than alkynes containing electron-withdrawing group. This methodology can be successfully applied to the formal synthesis of β-amyloid aggregation inhibitor 5-chloro-3-[4-(3-diethylaminopropoxy)benzoyl]-2-(4-methoxyphenyl)benzofuran.

4. Experimental

4.1. General

All reactions were carried out in reaction tubes under nitrogen atmosphere. Substituted *o*-Iodophenols, Ligands **L2**, **L3**, and **L4** were made using literature procedures. *o*-Iodophenol, aryl acetylenes, and copper(II) triflate were purchased from Aldrich Chemical Company. Potassium carbonate are purchased from Spectrochem India Private Limited and used without further purification. All other reagents are commercially available and were used without further purification. Toluene was purchased from SRL Chemicals, India and dried over sodium. Reaction temperatures were controlled by Varivolt temperature modulator. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence quenching. Silica gel for chromatography (particle size 100–200 mesh) was purchased from SRL India. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument. ^{1}H NMR spectra were reported relative to Me_4Si (δ 0.0 ppm) or residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrometer and are reported in frequency of

absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer. The Gas chromatography was a Agilent 6890N series with a HP capillary column.

4.2. Typical experimental procedure (Table 3, entry 1)

Typical Experimental Procedure: Dibenzyl-BINAM (23.2 mg, 0.05 mmol), $Cu(OTf)_2$ (18.1 mg, 0.05 mmol), K_2CO_3 (103.7 mg, 0.75 mmol), and *o*-iodophenol (55 mg, 0.25 mmol) were taken in a 10 mL reaction tube capped with a septum. The tube was evacuated and back-filled with nitrogen. Toluene (3 mL) was added to the reaction mixture at room temperature. Then the resulting solution refluxed, followed by phenyl acetylene (33 μL, 0.3 mmol) addition at refluxing temperature and the septum was replaced with a glass stopper and the reaction mixture was refluxed until the complete disappearance of *o*-iodophenol (TLC), then the reaction mixture was allowed to cool to room temperature and the solvent was evaporated. The crude residue was purified by column chromatography on silica gel using hexane as the eluent to afford 2-phenylbenzofuran **3** (43.7 mg, 90%) as a white solid. Mp 119 °C (lit. 120 °C)[17]; R_f 0.64 (hexanes); FTIR (neat) 3052, 2925, 2853, 1456, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, J=7.6 Hz), 7.59 (1H, d, J=7.6 Hz), 7.53 (1H, d, J=8.0 Hz), 7.45 (2H, t, J=8 Hz), 7.35 (1H, t, J=7.6 Hz), 7.32–7.20 (2H, m), 7.03 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.0, 130.6, 129.4, 128.9, 128.7, 125.1, 124.4, 123.1, 121.0, 111.3, 101.4; HRMS $[MNa]^+$ Calculated for $C_{14}H_{10}ONa$ 217.0629, found 217.0625.

*4.2.1. 2-p-Tolyl-benzo[b]furan (**5**).* White solid, mp 124–125 °C (lit. 126–128 °C)[12g]; R_f 0.64 (hexanes); FTIR (neat) 3029, 2917, 2852, 1451, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, J=8 Hz), 7.57–7.53 (1H, m), 7.50 (1H, d, J=8 Hz), 7.28–7.18 (4H, m), 6.95 (1H, s), 2.38 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 154.9, 138.7, 129.5, 129.6, 127.9, 125.0, 124.1, 123.0, 120.9, 111.2, 100.7, 21.5; HRMS $[MH]^+$ Calculated for $C_{15}H_{13}O$ 209.0966, found 209.0968.

*4.2.2. 2-m-Tolyl-benzo[b]furan (**6**).* White solid, mp 74–75 °C (lit. 75–76 °C)[24]; R_f 0.68 (hexanes); FTIR (neat) 3039, 2922, 2852, 1451, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, s), 7.67 (1H, d, J=7.6 Hz), 7.60–7.55 (1H, m), 7.52 (1H, d, J=7.6 Hz), 7.33 (1H, t, J=7.6 Hz), 7.30–7.19 (2H, m), 7.17 (1H, d, J=7.6 Hz), 7.01(1H, s), 2.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 155.0, 138.6, 130.5, 129.5, 129.4, 128.8, 125.7, 124.3, 123.0, 122.3, 121.0, 111.3, 101.3, 21.6; HRMS $[MH]^+$ Calculated for $C_{15}H_{13}O$ 209.0966, found 209.0968.

*4.2.3. 2-(4-Methoxy-phenyl)-benzo[b]furan (**7**).* White solid, mp 148–150 °C (lit. 146–147 °C)[12g]; R_f 0.2 (hexanes); FTIR (neat) 3054, 3006, 2961, 2837, 1454, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.77 (2H, m), 7.54 (1H, d, J=8.4 Hz), 7.49 (1H, d, J=8 Hz), 7.28–7.17 (2H, m), 7.01–6.94 (2H, m), 6.88 (1H, s), 3.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 156.2, 154.8, 129.6, 126.6, 123.9, 123.5, 123.0, 120.7, 114.4, 111.1, 99.8, 55.5; HRMS $[MH]^+$ Calculated for $C_{15}H_{13}O_2$ 225.0916, found 225.0918.

*4.2.4. 2-(4-Pentyl-phenyl)-benzo[b]furan (**8**).* White solid, mp 89–90 °C; R_f 0.65 (hexanes); FTIR (neat) 2956, 2928, 2856, 1452, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J=8 Hz), 7.59–7.55 (1H, m), 7.51 (1H, d, J=8 Hz), 7.29–7.19 (4H, m), 6.97 (1H, s), 2.64 (2H, t, J=8 Hz), 1.70–1.59 (2H, m), 1.42–1.28 (4H, m), 0.90 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 154.9, 143.8, 129.5, 129.0, 128.1, 125.1, 124.1, 123.0, 120.9, 111.2, 100.7, 35.9, 31.6, 31.2, 22.7, 14.2; HRMS $[MH]^+$ Calculated for $C_{19}H_{21}O$ 265.1592, found 265.1589.

*4.2.5. 2-(3-(Trifluoromethyl)-phenyl)-benzo[b]furan (**9**).* White solid, mp 65–67 °C (lit. 67.2–67.6 °C)[25]; R_f 0.8 (hexanes); FTIR (neat) 3110, 3069, 3038, 1450, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, s), 8.00 (1H, d, J=7.6 Hz), 7.64–7.50 (4H, m), 7.36–7.28 (1H, m), 7.26–7.22 (1H, m), 7.08 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 154.3, 131.7, 131.4, 129.5, 129.0, 128.0, 125.1, 125.1, 123.4, (q, J=3.9 Hz), 121.8, 121.8 (q, J=3.9 Hz), 121.4, 111.5, 102.8; HRMS $[MNa]^+$ Calculated for $C_{15}H_9ONaF_3$ 285.0503, found 285.0504.

*4.2.6. 2-(4-Fluorophenyl)benzo[b]furan (**10**).* Light yellow solid, mp 120–122 °C (lit. 122–124 °C)[26]; R_f 0.6 (5% ethyl acetate/hexanes); FTIR (neat) 3058, 2927, 839, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–7.80 (2H, m), 7.57 (1H, d, J=8 Hz), 7.51 (1H, d, J=8 Hz), 7.31–7.20 (2H, m), 7.17–7.10 (2H, m), 6.94 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J=247.1 Hz), 155.2, 155.0, 129.3, 126.9 (d, J=8 Hz), 124.4, 123.2, 121.0, 116.0 (d, J=21.8 Hz), 111.3, 101.1; HRMS $[MH]^+$ Calculated for $C_{14}H_{10}FO$ 213.0716, found 213.0718.

*4.2.7. 5-Methyl-2-phenyl-benzo[b]furan (**11**).* White solid, mp 131–133 °C (lit. 129 °C)[27]; R_f 0.58 (hexanes); FTIR (neat) 3062, 2920, 2855, 1444, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89–7.83 (2H, m), 7.49–7.30 (5H, m), 7.09 (1H, dd, J=8.4, 2 Hz), 2.44 (3H, s), 6.95 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 153.5, 132.5, 130.8, 129.5, 128.9, 128.6, 125.7, 125.0, 120.9, 110.8, 101.2, 21.5; HRMS $[MH]^+$ Calculated for $C_{15}H_{13}O$ 209.0966, found 209.0964.

*4.2.8. 5-tert-Butyl-2-phenyl-benzo[b]furan (**12**).* White solid, mp 100–102 °C (lit. 102–103 °C)[28]; R_f 0.63 (hexanes); FTIR (neat) 3061, 2957, 2866, 1474, 1278 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.84 (2H, m), 7.59 (1H, d, J=2 Hz), 7.48–7.42 (3H, m), 7.38–7.32 (2H, m), 7.00 (1H, s), 1.38 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 153.3, 146.1, 130.8, 129.0, 128.9, 128.5, 125.0, 122.4, 117.2, 110.6, 101.6, 34.9, 32.0; HRMS $[MH]^+$ Calculated for $C_{18}H_{19}O$ 251.1436, found 251.1432.

*4.2.9. 5-Chloro-2-phenyl-benzo[b]furan (**13**).* White solid, mp 154 °C (lit. 156 °C)[29]; R_f 0.68 (hexanes); FTIR (neat) 3086, 2922, 1452, 1274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89–7.82 (2H, m), 7.55 (1H, d, J=2 Hz), 7.50–7.41 (3H, m), 7.41–7.35 (1H, m), 7.23 (1H, dd, J=8.8, 2 Hz), 6.97 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 153.4, 130.7, 130.1, 129.1, 129.0, 128.6, 125.2, 124.5, 120.6, 112.3, 100.9; HRMS $[MH]^+$ Calculated for $C_{14}H_{10}ClO$ 229.0420, found 229.0423.

*4.2.10. 5-Chloro-2-p-tolyl-benzo[b]furan (**14**).* White solid, mp 175–176 °C (lit. 177–178 °C)[10]; R_f 0.83 (hexanes); FTIR (neat) 3029, 2915, 2857, 1444, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, J=8.0 Hz), 7.50 (1H, d, J=2 Hz), 7.40 (1H, d, J=8.4 Hz), 7.24 (2H, d, J=8 Hz), 7.20 (1H, dd, J=8.8, 2 Hz), 6.87 (1H, s), 2.39 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 153.3, 139.3, 130.9, 129.7, 128.5, 127.4, 125.1, 124.2, 120.4, 112.1, 100.2, 21.5; HRMS $[MH]^+$ Calculated for $C_{15}H_{13}OCl$ 244.0655, found 244.0661.

*4.2.11. 5-Chloro-2-m-tolyl-benzo[b]furan (**15**).* White solid, mp 98–100 °C; R_f 0.89 (hexanes); FTIR (neat) 3109, 3059, 3038, 2920, 2860, 1443, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, s), 7.64 (1H, d, J=7.6 Hz), 7.53 (1H, d, J=2.4 Hz), 7.42 (1H, d, J=8.4 Hz), 7.34 (1H, t, J=7.6 Hz), 7.22 (1H, dd, J=8.8, 2 Hz), 7.19 (1H, d, J=7.6 Hz), 6.93 (1H, s), 2.42 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 153.4, 138.7, 130.8, 130.0, 130.0, 128.9, 128.6, 125.8, 124.4, 122.4, 120.5, 112.2, 100.8, 21.6; HRMS $[MH]^+$ Calculated for $C_{15}H_{13}OCl$ 244.0655, found 244.0658.

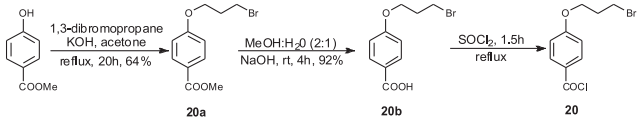
*4.2.12. 5-Chloro-2-(4-pentyl-phenyl)-benzo[b]furan (**16**).* White solid, mp 147–149 °C; R_f 0.71 (hexanes); FTIR (neat) 2931, 2858, 1444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, J=8 Hz), 7.50 (1H, d, J=2.4 Hz), 7.40 (1H, d, J=8.8 Hz), 7.25 (2H, d, J=8.0 Hz), 7.20 (1H, dd, J=8.8, 2 Hz), 6.87 (1H, s), 2.63 (2H, t, J=7.6 Hz), 1.64 (2H, quint, J=7.6 Hz), 1.41–1.27 (4H, m), 0.90 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 153.3, 144.4, 130.9, 129.1, 128.5, 127.6,

125.2, 124.2, 120.4, 112.1, 100.2, 35.9, 31.6, 31.1, 22.7, 14.2; HRMS $[MH]^+$ Calculated for $C_{19}H_{20}OCl$, 299.1203; found 299.1201.

4.3. Formal synthesis of 5-chloro-3-[4-(3-diethylamino-propoxy)-benzoyl]-2-(4-methoxyphenyl)-benzofuran

*4.3.1. 4-Chloro-2-iodophenol (**17**)*[30]. White solid, mp 77 °C (lit. 78 °C); R_f 0.38 (5% ethyl acetate/hexanes); FTIR (neat) 3315, 3086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, d, J=2.4 Hz), 7.22 (1H, dd, J=8.8, 2.4 Hz), 6.92 (1H, d, J=8.8 Hz), 5.28 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 137.3, 130.3, 126.2, 115.8, 85.6.

*4.3.2. 4-(3-Bromopropoxy)benzoyl chloride (**20**)*[23].



*4.3.2.1. Methyl 4-(3-bromopropoxy)benzoate (**20a**).* In a 100 mL two neck round bottom flask equipped with reflux condenser methyl *p*-hydroxy benzoate (1.52 g, 10 mmol), 1,3-dibromopropane (3.23 g, 16 mmol), and K_2CO_3 (1.66 g, 12 mmol) were taken, acetone (30 mL) was added to the round bottom flask. The contents were refluxed for 20 h. The reaction mixture was cooled to room temperature, the crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes as eluents. The reaction provided 64% yield (1.74 g) of methyl 4-(3-bromopropoxy) benzoate **20a** as white solid, mp 64–65 °C; R_f 0.64 (10% ethyl acetate/hexanes); FTIR (neat): 2948, 1718, 1606, 1510, 1435, 1256, 1169, 1108, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–7.97 (2H, m), 6.92 (2H, d, J=8.8 Hz), 4.16 (2H, t, J=6.0 Hz), 3.88 (3H, s), 3.60 (2H, t, J=6.0 Hz), 2.34 (2H, quint, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 162.5, 131.7, 123.0, 114.2, 65.6, 52.0, 32.3, 29.8; HRMS $[MH]^+$ Calculated. for $C_{11}H_{14}O_3Br$, 273.0126; found 273.0125.

*4.3.2.2. 4-(3-Bromopropoxy)benzoic acid (**20b**).* In a 50 mL round bottom flask methyl 4-(3-bromopropoxy)benzoate **20a** (1.36 g, 5 mmol), NaOH (1.20 g, 30 mmol) were taken, methanol (10 mL) and water (5 mL) was added to the round bottom flask. The contents were stirred for 4 h at room temperature. Then, the methanol was evaporated and the reaction mixture was washed with methylene chloride. The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid, extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was recrystallized from isopropanol to give 4-(3-Bromopropoxy)benzoic acid **20b** (1.19 g, 92%) as white solid, mp 154–156 °C; R_f 0.82 (50% ethyl acetate/hexanes); FTIR (neat): 2985, 1737, 1680, 1607, 1511, 1430, 1246, 1171, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (2H, d, J=8.8 Hz), 6.96 (2H, d, J=8.8 Hz), 4.19 (2H, t, J=6.0 Hz), 3.61 (2H, t, J=6.4 Hz), 2.35 (2H, quint, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 163.3, 132.6, 122.1, 114.4, 65.7, 32.3, 29.8; HRMS $[MH]^+$ Calculated for $C_{10}H_{12}O_3Br$, 258.9970; found 258.9965.

*4.3.2.3. 4-(3-Bromopropoxy)benzoyl chloride (**20**).* In a 5 mL round bottom flask 4-(3-bromopropoxy)benzoic acid **20b** (516 mg, 2 mmol) was taken to this 1 mL of thionyl chloride added and refluxed for 90 min. The reaction was monitored by TLC, excess thionyl chloride was removed under reduced pressure to give 4-(3-bromopropoxy)benzoyl chloride **20** (500 mg) was used for the next step in its crude form without further purification.

*4.3.2.4. 5-Chloro-2-(4-methoxyphenyl)-benzofuran (**19**).* Dibenzyl-BINAM (185.6 mg, 0.4 mmol), $Cu(OTf)_2$ (144.7 mg, 0.4 mmol), K_2CO_3 (830 mg, 6 mmol), and *o*-iodophenol (508 mg, 2.0 mmol) were taken in a reaction tube capped with a septum. The tube was evacuated and back-filled with nitrogen. Toluene (3 mL) was added to the reaction mixture at room temperature. Then the resulting solution refluxed, followed by 1-ethynyl-4-methoxybenzene **18** (311 μL, 2.4 mmol) addition at refluxing temperature and the septum was replaced with a glass stopper and the reaction mixture was refluxed until the complete disappearance of *o*-iodophenol (TLC). Then the reaction mixture was allowed to cool to room temperature and the solvent was evaporated. The crude residue was purified by column chromatography on silica gel using hexane as the eluent to afford 5-chloro-2-(4-methoxyphenyl)-benzofuran **19** (413.6 mg, 80%) as white solid. Mp 164–165 °C (lit. 166–167 °C)[10]; R_f 0.60 (hexanes); FTIR (neat) 3036, 2918, 2851, 1485, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J=8.8 Hz), 7.50 (1H, d, J=2 Hz), 7.40 (1H, d, J=8.8 Hz), 7.19 (1H, dd, J=8.6, 2 Hz), 6.98 (2H, d, J=8.8 Hz), 6.82 (1H, s), 3.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 157.7, 153.2, 131.0, 128.5, 126.7, 124.0, 123.0, 120.2, 114.5, 112.0, 99.3, 55.5; GC–MS EI^+: m/z=258.0259.

*4.3.2.5. 5-Chloro-3-[4-(3-bromopropoxy)benzoyl]-2-(4-methoxyphenyl) benzofuran (**21**).*[23]. Stannic chloride (469 mg, 1.8 mmol) was added to a stirred solution of 5-chloro-2-(4-methoxyphenyl)-benzofuran **19** (388 mg, 1.5 mmol) and 4-(3-bromopropoxy)benzoyl chloride **20** (500 mg, 1.8 mmol) in benzene (12 mL) at room temperature under nitrogen atmosphere, and the stirring was continued at the same temperature for 24 h. The reaction mixture was quenched by the addition of water. The organic layer was dried over anhydrous Na_2SO_4, and was concentrated under the reduced pressure. The residue was purified by column chromatography using ethyl acetate/hexanes as eluents. The reaction provided **21** (420 mg, 56%) as a oily liquid, R_f 0.38 (10% ethyl acetate/hexanes); FTIR (neat): 2924, 1646, 1601, 1504, 1447, 1366, 1308, 1258, 1173, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (2H, d, J=8.8 Hz), 7.61–7.55 (2H, m), 7.41–7.37 (2H, m), 7.23–7.19 (1H, m), 6.80–6.75 (4H, m), 4.09 (2H, t, J=6.0 Hz), 3.74 (3H, s), 3.67 (2H, t, J=6.0 Hz), 2.18 (2H, quint, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 163.2, 161.1, 158.3, 152.1, 132.4, 130.7, 130.4, 130.0, 129.5, 125.2, 121.8, 120.9, 114.7, 114.5, 114.2, 112.2, 64.7, 55.5, 32.2, 29.8; HRMS $[MH]^+$ Calculated for $C_{25}H_{21}O_4ClBr$, 499.0312; found 499.0307.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.01.026.

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