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An Efficient Synthesis of Substituted Furans by Cupric Halide-Mediated Intramolecular Halocyclization of 2-(1-Alkynyl)-2-alken-1-ones

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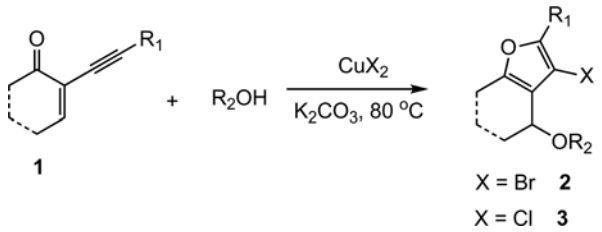
An efficient synthesis of 3-halofurans by the intramolecular cyclization of 2-(1-alkynyl)-2-alken-1-ones with cupric halide has been developed. A broad range of 3-chloro- and 3-bromofuran derivatives could be obtained in the present method in moderate to good yields. The 3-halofuran derivatives are potential synthetic intermediates for amplification of molecular complexity.

Key Words : Halofurans, Copper halide, Halogenation, Cyclization

Introduction

The construction of furan skeleton has attracted considerable attention due to their occurrence in numerous natural products.[1] Compounds with furan units have been used as flavor, fragrance substances, insecticides, and antileukemic agents.[2] Moreover, they are also found wide utility as synthetic intermediates for the preparation of a variety of heterocyclic and acyclic compounds. In particular, halofurans are of special interest because the halogen atom provide an opportunity for further functionalization by a variety of C-C, C-N, or C-S bond formation through the transition-metal-catalyzed reactions and also serve as building blocks in combinatorial chemistry.[3] Therefore, numerous synthetic methods have been developed from time to time in order to improve the efficiency of the synthesis of furan skeleton.[4] Among them, the intramolecular electrophilic cyclization of functionally substituted alkynes are the most extensively studied approaches to afford the halofuran skeleton.[5] Recently, Liu reported the electrophilic cyclizations of 2-(1-alkynyl)-2-alken-1-ones to synthesize 3-iodofurans using I_2/K_3PO_4.[6] However, the synthesis of 3-chloro- and 3-bromofurans starting from 2-(1-alkynyl)-2-alken-1-ones was rarely reported probably because the stability of the corresponding halonium intermediates decreases in the order I > Br > Cl.[7] Thus, it is highly desired to develop efficient and general synthetic methods for access to chloro- and bromofurans in order to build up these molecules in a combinatorial format.

CuX_2-mediated the intramolecular annulation of alkynes or allenes has proven to be extremely effective for the synthesis of a wide variety of carbocycles and heterocycles.[8] Many important heterocycles, such as selenophenes, thiophenes, indoles, butenolides, phosphaisocoumarins, 2,5-dihydro[1,2] oxaphosphole 2-oxides, azaanthraquinones, 5-hydroxypyrrol-2(5*H*)-ones, benzo[*b*]thiophenes have been synthesized based on this strategy. Very recently, our group reported a convenient one-pot domino processes for the synthesis of highly functionalized polysubstituted furan derivatives through CuX_2-mediated cyclization of 1-(1-alkynyl)-cyclopropyl ketones.[9] Prompted by these results, we envisioned that 2-(1-alkynyl)-2-alken-1-ones[10] could be also utilized as starting material for synthesis of furan derivatives due to the structural similarity with 1-(1-alkynyl)-cyclopropyl ketones. On the basis of our present interest on developing new strategies toward heterocycles,[11] we herein report a highly efficient and general method for the generation of functionalized furans *via* sequential electrophilic cyclization-addition-reductive elimination reaction of 2-(1-alkynyl)-2-alken-1-ones under mild conditions (Scheme 1).

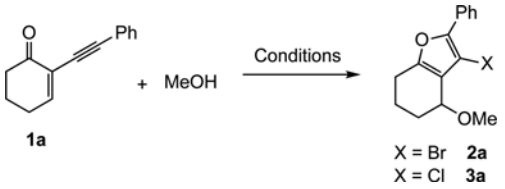


Scheme 1. CuX_2-mediated halocyclization of 2-(1-alkynyl)-2-alken-1-ones.

Results and Discussion

We initiated our study on the reaction of **1a** with $CuBr_2$ in the presence of various bases and in various solvents. In the absence of base, the desired furan product **2a** was isolated in only 48% yield (Table 1, entry 1). The addition of inorganic bases such as Na_2CO_3 and K_3PO_4 increased the yield of **2a** to 74% and 65%, respectively (Table 1, entries 2 and 3). Interestingly, with K_2CO_3 as the base, product **2a** was isolated in 82% yield in a shorter reaction time (Table 1, entry 4). When the reaction was performed with the organic base Et_3N, only a moderate yield of the product was obtained (Table 1, entry 5). Further screening showed that acetonitrile was a suitable solvent, other solvents such as DCE, DMSO, or CH_3OH did not improve the yield (Table 1, entries 6-9). Additionally, $CuCl_2$ could be used to generate chlorofuran

Table 1. Optimized conditions in the halocyclization of **1a**[a]



Entry	CuX_2	Base	Solvent	Time (h)	Yield (%)[b]
1	$CuBr_2$	-	CH_3CN	6	48
2	$CuBr_2$	Na_2CO_3	CH_3CN	4	74
3	$CuBr_2$	K_3PO_4	CH_3CN	6	65
4	$CuBr_2$	K_2CO_3	CH_3CN	3	82
5	$CuBr_2$	Et_3N	CH_3CN	6	56
6	$CuBr_2$	K_2CO_3	DMSO	6	71
7	$CuBr_2$	K_2CO_3	DCE	6	60
8	$CuBr_2$	K_2CO_3	CH_3OH	3	76
9	$CuBr_2$	K_2CO_3	THF	6	47
10	$CuCl_2$	K_2CO_3	CH_3CN	6	73

[a]Reaction conditions: **1a** (0.5 mmol), MeOH (10 equiv.), Base (2 equiv), CuX_2 (2.5 equiv), solvent (5 mL) at 80 °C. [b]Isolated yield.

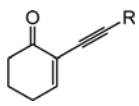
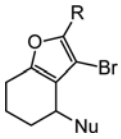
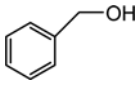
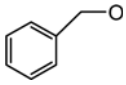
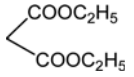
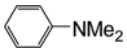
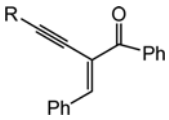
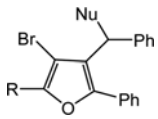
3a.

With the optimal conditions in hand, the scope of nucleophiles was probed. It was found that, in addition to methanol, secondary alcohol *i*-PrOH or benzyl alcohol could be used as effective nucleophile for this reaction (Table 2, entries 2-3). However, the use of propargylic alcohol or allylic alcohol resulted in no reaction (data not shown). Unfortunately, in the case of malonate and *N*,*N*-dimethylaniline, compound **2d** was isolated, indicating that malonate and *N*,*N*-dimethylaniline are not suitable nucleophiles in this reaction (Table 2, entries 4-5). The application scope of the reaction was further investigated with various alkyne derivatives under the optimized conditions. Substrates with either electron-donating or -withdrawing substituents in the *para*-position were found to be reactive under these conditions, giving the desired products **2e-g** in good yields (Table 2, entries 6-8). Likewise, this reaction was also sustainable with alkyl **1e** and **1j** as substituents. However, when alkyne of **1f** bearing a TMS group was checked, none of the product was isolated (Table 2, entry 10). Acyclic substrate **1h-1j** also underwent a smooth annulation reaction with MeOH to produce furans **2i-2k** in moderate yields under these reaction conditions (Table 2, entries 11-13).

The generality of the method was also investigated using $CuCl_2$ with 2-(1-alkynyl)-2-alken-1-ones under the optimized conditions and the expected products chlorofurans **3a-3h** were obtained in moderate yields. As shown in Table 3, $CuCl_2$-mediated the intramolecular annulation of 2-(1-alkynyl)-2-alken-1-ones generally showed lowered reactivity as evidenced by the lower yields than that of $CuBr_2$ mediated reactions.

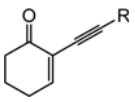
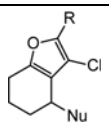
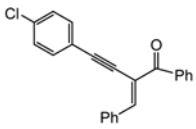
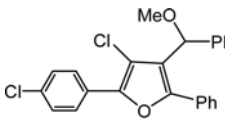
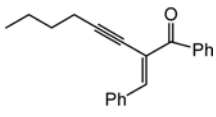
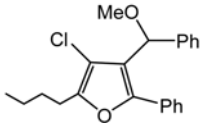
To further demonstrate the potential of 3-halofurans as precursors for compounds with increasing molecular complexity, we tested the reactivity of these compounds in palladium-catalyzed Sonogashira reaction. The reaction of **2a** with 1-

Table 2. $CuBr_2$-mediated bromocyclization of 2-(1-alkynyl)-2-alken-1-ones[a]

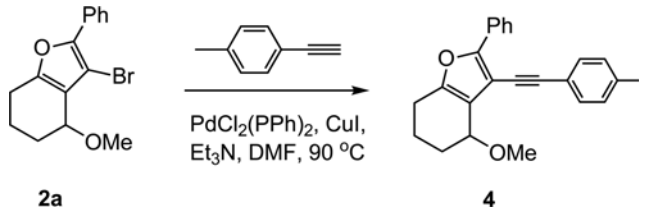
Entry	Substrate	NuH	Product	Yield (%)[b]
				
1	R=Ph (**1a**)	MeOH	Nu=MeO	**2a**, 82
2	**1a**	*i*-PrOH	*i*-PrO	**2b**, 70
3	**1a**			**2c**, 58
4	**1a**		Br	**2d**, 45
5	**1a**		Br	**2d**, 43
6	R=*p*-$MeOC_6H_4$ (**1b**)	MeOH	MeO	**2e**, 85
7	R=*p*-MeC_6H_4 (**1c**)	MeOH	MeO	**2f**, 87
8	R=*p*-ClC_6H_4 (**1d**)	MeOH	MeO	**2g**, 80
9	R=*n*-C_4H_9 (**1e**)	MeOH	MeO	**2h**, 68
10	R=TMS (**1f**)	MeOH	MeO	-[c]
				
11	R=*p*-MeC_6H_4 (**1h**)	MeOH	MeO	**2i**, 77
12	R=*p*-ClC_6H_4 (**1i**)	MeOH	MeO	**2j**, 72
13	R=*n*-C_4H_9 (**1j**)	MeOH	MeO	**2k**, 81

[a]Reaction conditions: **1** (0.5 mmol), NuH (10 equiv), K_2CO_3 (2 equiv), $CuBr_2$ (2.5 equiv) in CH_3CN (5.0 mL). [b]Isolated yield. [c]A complicated reaction mixture was formed.

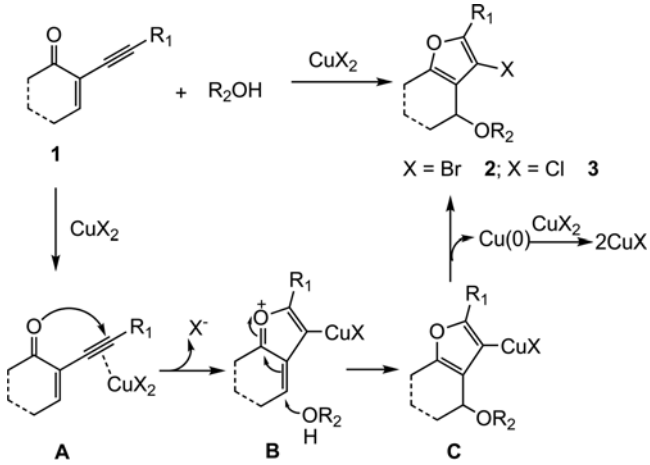
Table 3. $CuCl_2$-mediated chlorocyclization of 2-(1-alkynyl)-2-alken-1-ones[a]

Entry	Substrate	NuH	Product	Yield (%)[b]
				
1	R=Ph (**1a**)	MeOH	Nu=MeO	**3a**, 69
2	**1a**	*i*-PrOH	*i*-PrO	**3b**, 55
3	R=*p*-$MeOC_6H_4$ (**1b**)	MeOH	MeO	**3c**, 76
4	R=*p*-MeC_6H_4 (**1c**)	MeOH	MeO	**3d**, 73
5	R=*p*-ClC_6H_4 (**1d**)	MeOH	MeO	**3e**, 70
6	R=*n*-C_4H_9 (**1e**)	MeOH	MeO	**3f**, 66
7				**3g**, 70
8				**3h**, 61

[a]Reaction conditions: **1** (0.5 mmol), NuH (10 equiv), K_2CO_3 (2 equiv), $CuCl_2$ (2.5 equiv) in CH_3CN (5.0 mL). [b]Isolated yield.



Scheme 2. Sonogashira coupling reaction of **2a**.



Scheme 3. Plausible reaction mechanism.

ethynyl-4-methylbenzene gave the corresponding product **4** in 45% yield (Scheme 2).

Based on the above results and related literature,[8e,9] a plausible reaction mechanism is depicted in Scheme 3. CuX_2 species first coordinates to the triple bond to generate an intermediate **A**, which enhances the electrophilicity of the alkyne. The anti attack of the oxygen onto the activated triple bond led to the formation of intermediate **B**, which could be attacked by nucleophile in a regioselective Michael-type addition to afford intermediate **C**. Reductive elimination of **C** provides the 3-halofurans **2 or 3** and Cu(0). The formed Cu(0) can be oxidized by CuX_2 to produce CuX.

Conclusion

In conclusion, we have described a convenient and one-step synthesis of 3-halofurans *via* cupric halide-mediated annulation of 2-(1-alkynyl)-2-alken-1-ones. The reactions proceeded smoothly to afford the halofurans in moderate to good yields. Further application of this synthetic methodology in the synthesis of organic intermediates is currently in progress in our laboratory.

Experimental Section

General Procedure for the $CuBr_2$-Mediated Cyclization of 2-(1-Alkynyl)-2-alken-1-ones. To a solution of 2-(1-alkynyl)-2-alken-1-ones **1** (0.5 mmol) in CH_3CN (5 mL) was added MeOH (10 equiv), K_2CO_3 (2 equiv) and copper(II) bromide (2.5 equiv). The resulting mixture was stirred at 80 °C for 3 h, then the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether and the combined organic layers were dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel.

3-Bromo-4,5,6,7-tetrahydro-4-methoxy-2-phenylbenzofuran (2a): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.93 (d, J = 7.2 Hz, 2 H), 7.37-7.41 (t, J = 7.2 Hz, 2 H), 7.28-7.30 (t, J = 7.2 Hz, 1 H), 4.25 (s, 1 H), 3.49 (s, 3 H), 2.71-2.74 (m, 1 H), 2.52-2.60 (m, 1 H), 2.03-2.16 (m, 2 H), 1.86-1.89 (m, 1 H), 1.55-1.61 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 147.4, 130.3, 128.5, 127.7, 125.5, 121.1, 97.8, 70.8, 57.1, 27.4, 23.4, 18.1. MS: *m/z* (%) = 306 (100) [M^+]. $C_{15}H_{15}BrO_2$: calcd. C 58.65, H 4.92; found C 58.93, H 5.20.

3-Bromo-4,5,6,7-tetrahydro-4-isopropoxy-2-phenylbenzofuran (2b): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.90 (d, J = 7.6 Hz, 2 H), 7.36-7.40 (t, J = 7.6 Hz, 2 H), 7.25-7.29 (t, J = 7.6 Hz, 1 H), 4.43 (s, 1 H), 3.86-3.89 (m, 1 H), 2.69-2.74 (m, 1 H), 2.52-2.59 (m, 1 H), 2.05-2.09 (m, 2 H), 1.84-1.87 (m, 1 H), 1.55-1.61 (m, 1 H), 1.29-1.31 (d, J = 5.6 Hz, 3 H), 1.22-1.23 (d, J = 5.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 153.3, 147.3, 130.3, 128.5, 127.6, 125.5, 121.1, 97.7, 70.3, 67.2, 28.7, 23.9, 23.5, 22.7, 18.0. MS: *m/z* (%) = 334 (100) [M^+]. $C_{17}H_{19}BrO_2$: calcd. C 60.91, H 5.71; found C 61.12, H 6.02.

4-(Benzyloxy)-3-bromo-4,5,6,7-tetrahydro-2-phenylbenzofuran (2c): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.96 (m, 2 H), 7.24-7.55 (m, 8 H), 6.92-6.94 (d, J = 8.0 Hz, 2 H), 4.75 (s, 2 H), 4.20 (s, 1 H), 2.70-2.75 (m, 1 H), 2.52-2.61 (m, 1 H), 2.02-2.19 (m, 2 H), 1.85-1.92 (m, 1 H), 1.53-1.62 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 148.9, 137.2, 130.5, 128.6, 128.5, 128.4, 128.1, 127.8, 125.6, 118.9, 99.6, 72.5, 70.6, 27.6, 23.5, 18.2. MS: *m/z* (%) = 382 (100) [M^+]. $C_{21}H_{19}BrO_2$: calcd. C 65.81, H 5.00; found C 65.48, H 5.46.

3,4-Dibromo-4,5,6,7-tetrahydro-2-phenylbenzofuran (2d): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.90 (d, J = 7.2 Hz, 2 H), 7.38-7.43 (t, J = 7.2 Hz, 2 H), 7.27-7.32 (m, 1 H), 4.63 (s, 1 H), 2.72-2.76 (m, 1 H), 2.54-2.60 (m, 1 H), 2.02-2.15 (m, 2 H), 1.88-1.93 (m, 1 H), 1.52-1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 147.1, 135.8, 131.4, 128.5, 126.7, 121.4, 100.1, 51.2, 29.9, 28.4, 19.0. MS: *m/z* (%) = 354 (100) [M^+]. $C_{14}H_{12}Br_2O$: calcd. C 47.23, H 3.40; found C 47.68, H 3.71.

3-Bromo-4,5,6,7-tetrahydro-4-methoxy-2-(4-methoxyphenyl) benzofuran (2e): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.85 (d, J = 8.0 Hz, 2 H), 6.92-6.94 (d, J = 8.0 Hz, 2 H), 4.23 (s, 1 H), 3.82 (s, 3 H), 3.48 (s, 3 H), 2.68-2.72 (m, 1 H), 2.50-2.58 (m, 1 H), 2.01-2.15 (m, 2 H), 1.87 (bs, 1 H), 1.54-1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 152.6, 147.5, 127.1, 123.1, 120.8, 113.9, 96.2, 70.8, 57.1, 55.4, 27.4, 23.4, 18.1. MS: *m/z* (%) = 336 (100) [M^+]. $C_{16}H_{17}BrO_3$: calcd. C 56.99, H 5.08; found C 57.22, H 5.34.

3-Bromo-4,5,6,7-tetrahydro-4-methoxy-2-p-tolylbenzofuran (2f): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.81 (d, J = 7.6 Hz, 2 H), 7.19-7.21 (d, J = 7.6 Hz, 2 H), 4.24 (s, 1 H), 3.48 (s, 3 H), 2.69-2.73 (m, 1 H), 2.51-2.59 (m, 1 H), 2.35 (s, 3 H), 2.02-2.15 (m, 2 H), 1.87 (bs, 1 H), 1.54-1.60 (m, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 147.6, 137.6, 129.2, 127.5, 125.5, 120.9, 97.1, 70.8, 57.1, 27.4, 23.4, 21.4, 18.1. MS: *m/z* (%) = 320 (100) [M^+]. $C_{16}H_{17}BrO_2$: calcd. C 59.83, H 5.33; found C 60.14, H 5.61.

3-Bromo-2-(4-chlorophenyl)-4,5,6,7-tetrahydro-4-methoxybenzofuran (2g): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.87 (d, *J* = 8.0 Hz, 2 H), 7.34-7.36 (d, *J* = 8.0 Hz, 2 H), 4.24 (s, 1 H), 3.48 (s, 3 H), 2.69-2.75 (m, 1 H), 2.55-2.59 (m, 1 H), 2.01-2.17 (m, 2 H), 1.85-1.87 (m, 1 H), 1.54-1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 146.4, 133.4, 128.8, 126.6, 121.3, 98.3, 70.7, 57.1, 27.3, 23.4, 18.1. MS: *m/z* (%) = 340 (100) [M^+]. $C_{15}H_{14}BrClO_2$: calcd. C 52.74, H 4.13; found C 52.99, H 4.35

3-Bromo-2-butyl-4,5,6,7-tetrahydro-4-methoxybenzofuran (2h): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (s, 1 H), 3.44 (s, 3 H), 2.57-2.61 (m, 3 H), 2.41-2.49 (m, 1 H), 1.96-2.08 (m, 2 H), 1.81 (bs, 1 H), 1.50-1.59 (m, 3 H), 1.29-1.38 (m, 2 H), 0.89-0.93 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 151.4, 118.7, 97.3, 70.9, 57.0, 30.2, 27.6, 26.0, 23.4, 22.3, 18.2, 13.9. MS: *m/z* (%) = 286 (100) [M^+]. $C_{13}H_{19}BrO_2$: calcd. C 54.37, H 6.67; found C 54.60, H 6.95.

3-Bromo-4-(methoxy(phenyl)methyl)-5-phenyl-2-*p*-tolylfuran (2i): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.97 (d, *J* = 8.0 Hz, 2 H), 7.69-7.71 (d, *J* = 8.0 Hz, 2 H), 7.43-7.45 (d, *J* = 8.0 Hz, 2 H), 7.43-7.45 (m, 8 H), 5.74 (s, 1 H), 3.39 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 148.4, 140.0, 138.2, 130.0, 129.3, 128.4, 128.2, 127.4, 127.3, 126.9, 126.7, 125.8, 121.4, 99.6, 77.3, 56.9, 21.4. MS: *m/z* (%) = 432 (100) [M^+]. $C_{25}H_{21}BrO_2$: calcd. C 69.29, H 4.88; found C 69.71, H 4.55.

3-Bromo-2-(4-chlorophenyl)-4-(methoxy(phenyl)methyl)-5-phenylfuran (2j): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-8.02 (d, *J* = 8.0 Hz, 2 H), 7.68-7.70 (d, *J* = 8.0 Hz, 2 H), 7.19-7.44 (m, 10 H), 5.73 (s, 1 H), 3.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 147.2, 139.9, 134.0, 129.8, 129.3, 128.9, 128.7, 128.5, 128.3, 128.2, 127.6, 127.5, 127.0, 126.7, 121.7, 99.6, 100.6, 77.3, 57.0. MS: *m/z* (%) = 452 (100) [M^+]. $C_{24}H_{18}BrClO_2$: calcd. C 65.53, H 4.00; found C 65.78, H 4.36.

3-Bromo-2-butyl-4-(methoxy(phenyl)methyl)-5-phenylfuran (2k): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.60 (d, *J* = 7.6 Hz, 2 H), 7.39-7.41 (d, *J* = 7.6 Hz, 2 H), 7.21-7.33 (m, 6 H), 5.63 (s, 1 H), 3.37 (s, 3 H), 2.71-2.75 (t, *J* = 7.2 Hz, 2 H), 1.68-1.72 (m, 2 H), 1.38-1.43 (m, 2 H), 0.94-0.97 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 150.3, 140.2, 130.5, 128.4, 128.3, 128.0, 127.4, 127.0, 126.9, 119.5, 99.7, 77.45, 56.9, 29.9, 26.3, 22.4, 13.9. MS: *m/z* (%) = 340 (100) [M^+]. $C_{22}H_{23}BrO_2$: calcd. C 66.17, H 5.81; found C 66.48, H 5.62.

3-chloro-4,5,6,7-tetrahydro-4-methoxy-2-phenylbenzofuran (3a): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.88 (d, *J* = 7.6 Hz, 2 H), 7.37-7.40 (t, *J* = 7.2 Hz, 2 H), 7.24-7.26 (t, *J* = 8.0 Hz, 1 H), 4.31 (s, 1 H), 3.47 (s, 3 H), 2.68-2.73 (m, 1 H), 2.52-2.58 (m, 1 H), 2.03-2.14 (m, 2 H), 1.84-1.87 (m, 1 H), 1.55-1.62 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 145.9, 130.0, 128.6, 127.5, 125.0, 119.8, 111.9, 70.1, 56.9, 27.7, 23.4, 18.0. MS: *m/z* (%) = 262 (100) [M^+]. $C_{15}H_{15}ClO_2$: calcd. C 68.57, H 5.75; found C 68.79, H 5.98.

3-Chloro-4,5,6,7-tetrahydro-4-isopropoxy-2-phenylbenzofuran (3b): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.87 (d, *J* = 7.6 Hz, 2 H), 7.36-7.40 (t, *J* = 7.6 Hz, 2 H), 7.25-7.27 (m, 1 H), 4.48 (s, 1 H), 3.83-3.88 (m, 1 H), 2.68-2.72 (m, 1 H), 2.49-2.57 (m, 1 H), 2.03-2.09 (m, 2 H), 1.86 (bs, 1 H), 1.56-1.62 (m, 1 H), 1.27-1.29 (d, *J* = 5.6 Hz, 3 H), 1.22-1.23 (d, *J* = 5.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 145.9, 130.1, 128.5, 127.4, 124.9, 120.1, 111.8, 70.3, 66.5, 28.6, 23.7, 23.5, 22.6, 18.0. MS: *m/z* (%) = 290 (100) [M^+]. $C_{17}H_{19}ClO_2$: calcd. C 70.22, H 6.59; found C 70.01, H 6.80.

3-Chloro-4,5,6,7-tetrahydro-4-methoxy-2-(4-methoxyphenyl)benzofuran (3c): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.81 (d, *J* = 8.0 Hz, 2 H), 6.91-6.93 (d, *J* = 8.0 Hz, 2 H), 4.29 (s, 1 H), 3.81 (s, 3 H), 3.47 (s, 3 H), 2.67-2.72 (m, 1 H), 2.53-2.57 (m, 1 H), 2.01-2.13 (m, 2 H), 1.86 (bs, 1 H), 1.54-1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 152.1, 146.1, 126.5, 122.9, 119.5, 114.1, 110.2, 70.1, 56.9, 55.4, 27.7, 23.4, 18.0. MS: *m/z* (%) = 292 (100) [M^+]. $C_{16}H_{17}ClO_3$: calcd. C 65.64, H 5.85; found C 65.73, H 6.11.

3-Chloro-4,5,6,7-tetrahydro-4-methoxy-2-*p*-tolylbenzofuran (3d): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.52 (d, *J* = 7.2 Hz, 2 H), 7.14-7.16 (d, *J* = 7.2 Hz, 2 H), 4.28 (s, 1 H), 3.43 (s, 3 H), 2.69-2.73 (m, 1 H), 2.55-2.61 (m, 1 H), 2.33 (s, 3 H), 2.03 (bs, 1 H), 1.92 (bs, 1 H), 1.64-1.82 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 136.8, 129.4, 128.6, 123.5, 119.9, 104.7, 72.6, 56.2, 28.6, 23.4, 21.3, 19.0. MS: *m/z* (%) = 276 (100) [M^+]. $C_{16}H_{17}ClO_2$: calcd. C 69.44, H 6.19; found C 69.58, H 6.43.

3-Chloro-2-(4-chlorophenyl)-4,5,6,7-tetrahydro-4-methoxybenzofuran (3e): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.82 (d, *J* = 8.0 Hz, 2 H), 7.34-7.36 (d, *J* = 8.0 Hz, 2 H), 4.30 (s, 1 H), 3.47 (s, 3 H), 2.68-2.72 (m, 1 H), 2.50-2.58 (m, 1 H), 2.02-2.15 (m, 2 H), 1.87 (bs, 1 H), 1.55-1.62 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 145.0, 133.2, 128.8, 128.5, 126.1, 119.9, 112.4, 70.0, 57.0, 27.6, 23.4, 17.9. MS: *m/z* (%) = 296 (100) [M^+]. $C_{15}H_{14}Cl_2O_2$: calcd. C 60.62, H 4.75; found C 60.97, H 4.52.

2-Butyl-3-chloro-4,5,6,7-tetrahydro-4-methoxybenzofuran (3f): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (s, 1 H), 3.43 (s, 3 H), 2.53-2.60 (m, 3 H), 2.43-2.47 (m, 1 H), 1.96-2.07 (m, 2 H), 1.77-1.80 (m, 1 H), 1.51-1.59 (m, 3 H), 1.31-1.39 (m, 2 H), 0.89-0.93 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 149.6, 117.5, 110.8, 70.3, 56.8, 30.1, 27.9, 25.3, 23.4, 22.3, 18.1, 13.9. MS: *m/z* (%) = 242 (100) [M^+]. $C_{13}H_{19}ClO_2$: calcd. C 64.32, H 7.89; found C 64.79, H 7.50.

2-Butyl-3-chloro-4-(methoxy(phenyl)methyl)-5-phenylfuran (3h): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.60 (d, *J* = 6.8 Hz, 2 H), 7.40-7.42 (d, *J* = 7.2 Hz, 2 H), 7.21-7.34 (m, 6 H), 5.62 (s, 1 H), 3.38 (s, 3 H), 2.70-2.74 (t, *J* = 7.2 Hz, 2 H), 1.68-1.72 (m, 2 H), 1.38-1.43 (m, 2 H), 0.93-0.97 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 149.7, 140.3, 130.6, 128.5, 128.3, 128.1, 127.5, 127.0, 126.8, 118.8, 113.1, 76.92, 56.9, 29.9, 25.5, 22.4, 13.9. MS: *m/z* (%) = 354 (100) [M^+]. $C_{22}H_{23}ClO_2$: calcd. C 74.46, H 6.53; found C 74.81, H 6.23.

3-Chloro-2-(4-chlorophenyl)-4-(methoxy(phenyl)methyl)-5-phenylfuran (3g): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.97 (d, J = 8.0 Hz, 2 H), 7.69-7.71 (d, J = 8.0 Hz, 2 H), 7.24-7.45 (m, 10 H), 5.72 (s, 1 H), 3.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 145.8, 139.9, 133.9, 129.9, 128.9, 128.7, 128.6, 128.4, 128.0, 127.7, 127.4, 126.7, 126.5, 120.8, 114.3, 76.7, 57.2. MS: *m/z* (%) = 408 (100) [M^+]. $C_{24}H_{18}Cl_2O_2$: calcd. C 70.43, H 4.43; found C 70.88, H 4.15.

4,5,6,7-Tetrahydro-4-methoxy-2-phenyl-3-(2-*p*-tolylethynyl)benzofuran (4): Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.98 (d, J = 8.0 Hz, 2 H), 7.43-7.48 (m, 2 H), 7.23-7.41 (m, 3 H), 7.04-7.06 (d, J = 8.0 Hz, 2 H), 4.24 (s, 1 H), 3.47 (s, 3 H), 2.70-2.76 (m, 1 H), 2.52-2.62 (m, 1 H), 2.30 (s, 3 H), 2.05-2.16 (m, 2 H), 1.86-1.90 (m, 1 H), 1.59-1.65 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 149.1, 132.5, 130.8, 128.9, 128.5, 128.2, 127.6, 125.1, 121.2, 118.9, 104.1, 94.3, 83.7, 70.3, 57.2, 27.6, 24.1, 23.2, 18.0. MS: *m/z* (%) = 342 (100) [M^+]. $C_{24}H_{22}O_2$: calcd. C 84.18, H 6.48; found C 83.79, H 6.80.

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