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Synthesis of 2-(4-Hydroxyphenyl)benzofurans and Their Application to β-Amyloid Aggregation Inhibitor

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The facile synthesis of a series of 2-(4-hydroxyphenyl)benzofurans (**4a-e**) is described. The one-pot reaction of 4-substituted phenols with the chloride **1** in the presence of zinc chloride afforded 3-methylthio-2-(4-acetoxyphenyl)benzofurans (**2a-e**). The compounds **4a-e** were obtained from the hydrolysis of **2a-e** followed by the desulfurization of the resulting 3-methylthio-2-(4-hydroxyphenyl)benzofurans (**3a-e**). 5-Methyl-3-*p*-toluoyl-2-[4-(3-diethylaminopropoxy)phenyl]benzofuran (**7**), a β-amyloid aggregation inhibitor, was synthesized by three steps starting from **4a**.

Key words: 2-(4-Hydroxyphenyl)benzofurans, 3-Methylthio-2-(4-acetoxyphenyl)benzofurans, Zinc chloride, Desulfurization, 5-Methyl-3-*p*-toluoyl-2-[4-(3-diethylaminopropoxy)phenyl]benzofuran, β-Amyloid aggregation inhibitor

INTRODUCTION

The benzofuran ring system occurs widely in natural products as well as in synthetic substances, which have been reported to exhibit a variety of important pharmacological properties (Ward, 1997). Moreover, a series of benzofuran derivatives have been reported to inhibit the fibril formation in the β-amyloid peptide (Howlett *et al.*, 1999), which is believed to be the underlying cause of Alzheimer's disease (Hardy and Allsop, 1991; Kakizuka, 1998). Recently, an efficient method for synthesizing 2-arylbenzofurans by the Lewis acid-promoted reactions of substituted phenols with 1-acyl-1-chlorosulfides was reported (Choi *et al.*, 1999; Seo *et al.*, 2000). In addition, this method was applied to the total synthesis of a naturally occurring demethoxy egonol (Choi *et al.*, 2000) from *Styrax obassia* (Takanishi *et al.*, 1974) and a norneolignan (Choi *et al.*, 2002) from *Ratanhia* Radix (Amone *et al.*, 1988).

Here, we report the convenient synthesis of 2-(4-hydroxyphenyl)benzofurans (**4a-e**) using 4-substituted phenols and 1-acyl-1-chlorosulfide **1**. Regarding their application as a β-amyloid aggregation inhibitor with a 2-(4-hydroxyphenyl)benzofuran ring, we report the preparation of 5-methyl-3-*p*-toluoyl-2-[4-(3-diethylaminopropoxy)phenyl]benzofuran (**7**) and a preliminary investigation into the substituent effect relating to β-amyloid aggregation inhibition.

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MATERIALS AND METHODS

All the reagents and solvents were purchased from commercial supplies and used without purification. The melting points were measured by a Gallen-kamp capillary melting point apparatus and were uncorrected. The IR spectra were recorded on a JASCO FT-IR 300 E spectrometer. The ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were obtained on a JEOL JNM-ECP 400 NMR spectrometer using TMS as the internal standard. The MS spectra were obtained on a Hewlett Packard 5973 GC/MS system by an electron impact method. Silica gel 60 (70-230 mesh, E. Merck) was used for all the column chromatographic separations.

4'-Acetoxy-2-chloro-2-(methylthio)acetophenone (1)

N-Chlorosuccinimide (2.67 g, 20.0 mmol) was added to a stirred solution of 4'-acetoxy-2-(methylthio)acetophenone (4.48 g, 20.0 mmol) in carbon tetrachloride (90 mL) in small portions at 0°C with continuous stirring at room

temperature for 6 h. The precipitated succinimide was filtered and the solvent was removed *in vacuo*. The residual solid was recrystallized from isopropyl ether to give **1** (3.18 g, 62%) in a white solid. mp 53-54°C; IR (KBr) 1762 (CO), 1688 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.33 (s, 3H), 6.30 (s, 1H), 7.23 (d, *J*=8.76 Hz, 2H), 8.08 (d, *J*=8.76 Hz, 2H); EI-MS m/z 260 (M+2), 258 (M^+), 121 (100%).

General procedure for the synthesis of 5-alkyl-3-methylthio-2-(4-acetoxyphenyl)benzofurans (2)

$ZnCl_2$ (750 mg, 5.50 mmol) was added to a stirred solution of a 4-substituted phenol (5.0 mmol) and **1** (1.30 g, 5.0 mmol) in methylene chloride (30 mL) at 0°C under an Ar atmosphere, and with continuous stirring at the same temperature for 1 h. The reaction was quenched by adding water and the organic layer was separated. The aqueous layer was extracted with methylene chloride (20 mL). The combined extracts were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (benzene/acetone=9/1) and recrystallized from isopropyl ether to give compound **2** as white solids.

5-Methyl-3-methylthio-2-(4-acetoxyphenyl)benzofuran (2a)

Yield 63%; mp 131-132°C; IR (KBr) 1763 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.37 (s, 3H), 2.48 (s, 3H), 7.13 (dd, *J*=8.28 Hz and *J*=1.64 Hz, 1H), 7.21 (d, *J*=8.60 Hz, 2H), 7.37 (d, *J*=8.28 Hz, 1H), 7.49 (s, 1H), 8.32 (d, *J*=8.76 Hz, 2H); ^{13}C-NMR (100 MH z, $CDCl_3$) δ 18.4, 21.1, 21.4, 108.9, 110.8, 119.7, 121.6, 126.3, 128.2, 128.3, 131.1, 132.8, 150.9, 152.0, 154.6, 169.2.; EI-MS m/z 312 (M^+), 270 (100%).

5-Ethyl-3-methylthio-2-(4-acetoxyphenyl)benzofuran (2b)

Yield 66%; mp 86-87°C; IR (KBr) 1748 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J*=7.52 Hz, 3H), 2.33 (s, 3H), 2.38 (s, 3H), 2.79 (q, *J*=7.56 Hz, 2H), 7.17 (dd, *J*=8.32 Hz and *J*=1.92 Hz, 1H), 7.21 (d, *J*=8.84 Hz, 2H), 7.41 (d, *J*=8.32 Hz, 1H), 7.52 (s, 1H), 8.33 (d, *J*=8.80 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.3, 18.4, 21.2, 28.9, 109.0, 110.9, 118.6, 121.7, 125.4, 128.2, 128.3, 131.1, 139.5, 150.9, 152.2, 154.6, 169.4; EI-MS m/z 326 (M^+), 284 (100%).

5-Propyl-3-methylthio-2-(4-acetoxyphenyl)benzofuran (2c)

Yield 64%; mp 84-85°C; IR (KBr) 1759 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J*=7.32 Hz, 3H), 1.66-1.76 (m, 2H), 2.33 (s, 3H), 2.38 (s, 3H), 2.72 (t, *J*=7.36 Hz, 2H), 7.15 (dd, *J*=8.44 Hz and *J*=1.64 Hz, 1H), 7.21 (d, *J*=8.60 Hz, 2H), 7.40 (d, *J*=8.40 Hz, 1H), 7.49 (s, 1H), 8.32 (d, *J*=8.80 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8, 18.4, 21.2, 25.1, 38. 1, 108.9, 110.8, 119.2, 121.7, 125.9, 128.2, 128.3, 131.0, 137.8, 150.9, 152.2, 154.6, 169.2; EI-MS m/z 340 (M^+), 298 (100%).

5-*t*-Butyl-3-methylthio-2-(4-acetoxyphenyl)benzofuran (2d)

Yield 60%; mp 93-94°C; IR (KBr) 1757 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.33 (s, 3H), 2.38 (s, 3H), 7.21 (d, *J*=8.96 Hz, 2H), 7.41 (d, *J*=1.84 Hz, 1H), 7.43 (s, 1H), 7.69-7.70 (m, 1H), 8.33 (d, *J*=8.95 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.5, 21.2, 31.9, 34.8, 109.3, 110.6, 116.0, 121.7, 123.1, 128.2, 128.3, 130.6, 146.5, 150.9, 151.9, 154.7, 169.3; EI-MS m/z 354 (M^+), 312 (100%).

5-Chloro-3-methylthio-2-(4-acetoxyphenyl)benzofuran (2e)

Yield 43%; mp 127-128°C; IR (KBr) 1747 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.36 (s, 3H), 7.22 (d, *J*=8.76 Hz, 2H), 7.25-7.28 (m, 1H), 7.41 (d, *J*=8.76 Hz, 1H), 7.66 (s, 1H), 8.32 (d, *J*=8.60 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.4, 21.1, 108.8, 11 2.3, 119.6, 121.8, 125.3, 127.5, 128.4, 129.0, 132.6, 151.3, 151.9, 155.9, 169.1; EI-MS m/z 334 (M+2), 332 (M^+), 290 (100%).

General procedure for the synthesis of 5-alkyl-3-methylthio-2-(4-hydroxyphenyl)benzofurans (3)

A solution of compound **2** (3.0 mmol) in 2*N*-NaOH (15 mL) and methanol (15 mL) was stirred for 5 h at room temperature. The reaction was washed with methylene chloride (10 mL). The aqueous layer was acidified to pH 3-4 with HCl, extracted with methylene chloride (10 mL×2), and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (benzene/acetone=9/1) to give compound **3**.

5-Methyl-3-methylthio-2-(4-hydroxyphenyl)benzofuran (3a)

Yield 94%; mp 118-119°C; IR (KBr) 3230 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.47 (s, 3H), 5.29 (s, 1H), 6.92 (d, *J*=8.76 Hz, 2H), 7.10 (dd, *J*=8.44 Hz and *J*=1.32 Hz, 1H), 7.35 (d, *J*=8.44 Hz, 1H), 7.46 (s, 1H), 8.18 (d, *J*=8.92 Hz, 2H); ^{13}C-NMR (100 MH z, $CDCl_3$) δ 18.3, 21.4, 106.9, 110.6, 115.4, 119.5, 123.4, 125.8, 128.9, 131.2, 132.6, 151.9, 155.5, 156.1; MS m/z 270 (M^+, 100%).

5-Ethyl-3-methylthio-2-(4-hydroxyphenyl)benzofu ran (3b)

Yield 91%; mp 73-74°C; IR (KBr) : 3200 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J*=7.56 Hz, 3H), 2.36 (s,

3H), 2.77 (q, *J*=7.56 Hz, 2H), 5.24 (s, 1H), 6.93 (d, *J*=8.92 Hz, 2H), 7.13 (dd, *J*=8.28 Hz and *J*=1.84 Hz, 1H), 7.38 (d, *J*=8.28 Hz, 1H), 7.49 (s, 1H), 8.18 (d, *J*=8.92 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.3, 18.4, 28.9, 107.1, 110.8, 115.4, 11 8.3, 123.4, 124.8, 128.9, 131.2, 139.3, 151.9, 155.5, 156.1; EI-MS m/z 284 (M^+, 100%).

5-Propyl-3-methylthio-2-(4-hydroxyphenyl)benzofuran (3c)
Yield 92%; mp 76-77°C; IR (KBr) 3196 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J*=7.24 Hz, 3H), 1.66-1.76 (m, 2H), 2.36 (s, 3H), 2.71 (t, *J*=7.48 Hz, 2H), 5.18 (s, 1H), 6.93 (d, *J*=8.80 Hz, 2H), 7.11 (dd, *J*=8.32 Hz and *J*=1.72 Hz, 1H), 7.38 (d, *J*=8.32 Hz, 1H), 7.47 (s, 1H), 8.18 (d, *J*=8.96 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8, 18.4, 25.1, 38.1, 107.1, 110.7, 115.4, 118.9, 123.5, 125.3, 128.9, 131.2, 137.7, 152.0, 155.5, 156.1; EI-MS m/z 298 (M^+, 100%).

5-t-Butyl-3-methylthio-2-(4-hydroxyphenyl)benzofuran (3d)
Yield 90%; mp 109-110°C; IR (KBr) 3214 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.37 (s, 3H), 5.25 (s, 1H), 6.93 (d, *J*=8.92 Hz, 2H), 7.38 (d, *J*=1.96 Hz, 1H), 7.41 (d, *J*=8.56 Hz, 1H), 7.67 (s, 1H), 8.18 (d, *J*=8.88 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 1 8.4, 31.9, 34.8, 107.4, 110.5, 115.4, 115.8, 122.6, 123.4, 128.9, 130.8, 146.3, 151.7, 155.6, 156.18; EI-MS m/z 312 (M^+, 100%).

5-Chloro-3-methylthio-2-(4-hydroxyphenyl)benzofuran (3e)
Yield 92%; mp 137-138°C; IR (KBr) 3243 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 5.26 (s, 1H), 6.94 (d, *J*=8.76 Hz, 2H), 7.23 (dd, *J*=8.60 Hz and *J*=2.0 Hz, 1H), 7.38 (d, *J*=8.60 Hz, 1H), 7.63 (s, 1H), 8.18 (d, *J*=8.60 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.3, 106.9, 112.1, 115.5, 119.3, 122.8, 124.7, 128.84, 129.1, 132.8, 151.8, 156.5, 156.8; EI-M S m/z 292 (M+2), 290 (M^+), 240 (100%).

General procedure for the synthesis of 5-alkyl-2-(4-hydroxyphenyl)benzofurans (4)
Compound **3** (2.0 mmol) was heated under reflux for 2 h in ethanol (20 mL) containing Raney nickel (W-2, *ca.* 2.5 g). The Raney nickel was removed by filtration and the solvent was removed by evaporation. The residual solid was recrystallized from isopropanol to give compound **4**.

5-Methyl-2-(4-hydroxyphenyl)benzofuran (4a)
Yield 80%; mp 213-215°C; IR (KBr) 3404 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 2.35 (s, 3H), 6.89-6.93 (m, 3H), 7.02 (dd, *J*=8.20 Hz and *J*=1.36 Hz, 1H.), 7.30 (s, 1H), 7.33 (d, *J*=8.36 Hz, 1H), 7.72 (d, *J*=8.84 Hz, 2H), 8.66 (s, 1H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 29.7, 100.4, 111.6, 117.1, 121.8, 123.6, 126.2, 127.7, 131.2, 133.5, 154.4, 157.8, 159.5; EI-MS m/z 224 (M^+, 100%).

5-Ethyl-2-(4-hydroxyphenyl)benzofuran (4b)
Yield 82%; mp 177-179°C; IR (KBr) 3411 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 1.20 (t, *J*=7.68 Hz, 3H), 2.66 (q, *J*=7.56 Hz, 2H), 6.91 (d, *J*=8.68 Hz, 2H), 6.96 (s, 1H), 7.06 (dd, *J*=8.24 Hz and J=1.88 Hz, 1H), 7.34-7.37 (m, 2H), 7.72 (d, *J*=8.84 Hz, 1H), 8.64 (s, 1H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 17.2, 33.3, 100.5, 111.7, 117.1, 120.6, 123.6, 125.2, 127.7, 131.2, 140.3, 154.5, 157.8, 159.5; EI-MS m/z 238 (M^+), 223 (100%).

5-Propyl-2-(4-hydroxyphenyl)benzofuran (4c)
Yield 81%; mp 168-170°C; IR (KBr) 3398 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 0.89 (t, *J*=7.36 Hz, 3H), 1.57-1.67 (m, 2H), 2.61 (t, *J*=7.60 Hz, 2H), 6.91 (d, *J*=8.84 Hz, 2H), 6.95 (s, 1H), 7.04 (dd, *J*=8.32 Hz and *J*=1.72 Hz, 1H), 7.33 (s, 1H), 7.35 (d, *J*=8.68 Hz, 1 H), 7.72 (d, *J*= 8.72 Hz, 2H), 8.64 (s, 1H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 14.5, 26.3, 39.0, 100.5, 111.6, 117.1, 121.3, 123.6, 125.8, 127.7, 131.1, 138.5, 154.6, 157.8, 159.5; EI-MS m/z 252 (M^+), 223 (100%).

5-t-Butyl-2-(4-hydroxyphenyl)benzofuran (4d)
Yield 85%; mp 150-152°C; IR (KBr) 3371 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 1.32 (s, 9H), 6.91 (d, *J*= 8.84 Hz, 2H), 6.98 (s, 1H), 7.29 (dd, *J*=8.60 Hz and *J*= 2.04 Hz, 1 H), 7.37 (d, *J*=8.72 Hz, 1H), 7.55 (d, *J*=1.92 Hz, 1H), 7.72 (d, *J*=8.72 Hz, 2H), 8.65 (s, 1H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 32.6, 35.7, 100.8, 111.3, 117.1, 118.2, 122.9, 123.7, 12 7.7, 130.8, 147.1, 154.2, 157.8, 159.5; EI-MS m/z 266 (M^+), 251 (100%).

5-Chloro-2-(4-hydroxyphenyl)benzofuran (4e)
Yeld 78%; mp 215-217°C; IR (KBr) 3398 (OH) cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 6.93 (d, *J*=8.84 Hz, 2H), 7.02 (s, 1H), 7.20 (dd, *J*=8.56 Hz and *J*=2.16 Hz, 1H), 7.48 (d, *J*= 8.68 Hz, 1H), 7.55 (s, 1H), 7.74 (d, *J*=8.80 Hz, 2H), 8.74 (s, 1H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 100.2, 113.4, 117.2, 121.4, 122.8, 124.9, 128.1, 129.4, 132.7, 154.4, 159.5, 159.9; EI-MS m/z 246 (M+2), 244 (M^+, 100%).

5-Methyl-2-[4-(3-bromopropoxy)phenyl]benzofuran (5)
A mixture of compound **4a** (1.12 g, 5.0 mmol), 1,3-dibromopropane (1.62 g, 8.0 mmol), and K_2CO_3 (830 mg, 6.0 mmol) in acetone (30 mL) was refluxed for 20 h. The inorganic materials were removed by filtration and the solvent was evaporated off. The residue was purified by column chromatography (chloroform) and recrystallized from isopropyl ether to give compound **5** (1.07 g, 62%) as

a white solid. mp 152-153°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.30-2.37 (m, 2H), 2.43 (s, 3H), 3.61 (t, *J*=6.36 Hz, 2H), 4.14 (t, *J*=5.76 Hz, 2H), 6.80 (s, 1H), 6.95 (d, *J*=8.88 Hz, 2H), 7.05 (dd, *J*=8.32 Hz and *J*=1.60 Hz, 1H), 7.33 (s, 1H), 7.37 (d, *J*=8.32 Hz, 1H), 7.77 (d, *J*=8.76 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 29.9, 32.3, 65.4, 99.6, 110.5, 114.8, 120.4, 123.8, 125.00, 126.3, 129.5, 132.2, 153.1, 156.0, 158.9; EI-MS m/z 346 (M+2), 344 (M^+), 223 (100%).

5-Methyl-3-*p*-toluoyl-2-[4-(3-bromopropoxy)phenyl] benzofuran (6)

$SnCl_4$ (782 mg, 3.0 mmol) was added to a stirred solution of compound **5** (1.0 g, 2.9 mmol) and *p*-toluoyl chloride (464 mg, 3.0 mmol) in benzene (30 mL) at room temperature under an Ar atmosphere, with continuous stirring at the same temperature for 24 h. The mixture was washed with 10% Na_2CO_3 (20 mL×2) and water (20 mL ×2). The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (benzene) to give compound **6** (725 mg, 54%) as a high viscous oil. IR (neat) 1648 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24-2.31 (m, 2H), 2.36 (s, 3 H), 2.38 (s, 3H), 3.56 (t, *J*=6.36 Hz, 2H), 4.06 (t, *J*=5.96 Hz, 2H), 6.80 (d, *J*=9.0 Hz, 2H), 7. 10-7.17 (m, 3H), 7.29 (s, 1H), 7.41 (d, *J*=8.32 Hz, 1H), 7.62 (d, *J*=8.92 Hz, 2H), 7.76 (d, *J*= 8.20 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 21.7, 29.7, 32.2, 65.3, 110.5, 114.4, 114. 9, 120.9, 122.5, 126.1, 128.8, 129.1, 129.8, 129.9, 133.2, 135.3, 143.9, 152.0, 157.2, 159.6, 19 2.2; MS m/z 464 (M+2), 462 (M^+), 119 (100%).

5-Methyl-3-*p*-toluoyl-2-[4-(3-diethylaminopropoxy) phenyl]benzofuran (7)

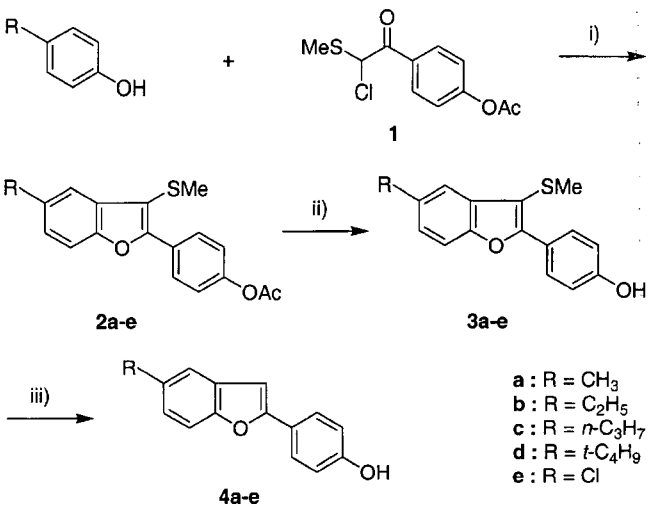
A mixture of compound **6** (650 mg, 1.40 mmol) and diethylamine (260 mg, 3.5 mmol) in ethanol (30 mL) was refluxed for 20 h. The reaction mixture was concentrated under reduced pressure and quenched by adding water (30 mL). The aqueous solution was adjusted to pH 10 with 10% KOH solution, and extracted with methylene chloride (20 mL×2). The combined extracts were dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by column chromatography (methanol) to give compound **7** (370 mg, 58%) as a high viscous oil. IR (neat) 1647 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02 (t, *J*= 7.04 Hz, 6H), 1.87-1.94 (m, 2H), 2.36 (s, 3H), 2.39 (s, 3H), 2.54 (q, *J*=7.16 Hz, 4H), 2.59 (t, *J*=7.04 Hz, 2H), 3.99 (t, *J*=6.32 Hz, 2H), 6.79 (d, *J*=8.92 Hz, 2H), 7.10-7.15 (m, 3H), 7.29 (s, 1H), 7.42 (d, *J*=8.40 Hz, 1H), 7.60 (d, *J*=8.92 Hz, 2H), 7.76 (d, *J*=8.28 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.7, 21.4, 21.7, 26.9, 46.9, 49.2, 66.4, 110.5, 114.4, 114.7, 120.9, 122.1, 126.0, 128.8, 129.1, 129.7, 130.1, 133.2, 135.3, 143.9, 152.0, 157.5, 160.1, 192.2; EI-MS m/z 455 (M^+), 246 (100%).

RESULTS AND DISCUSSION

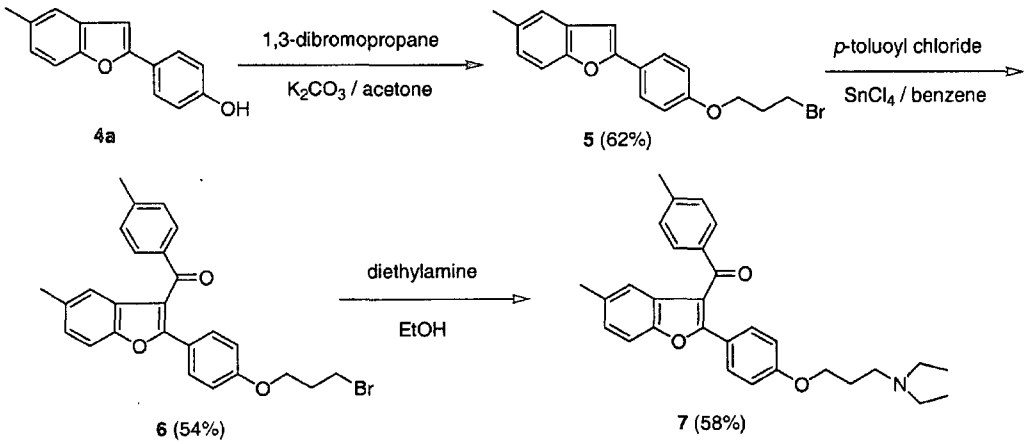
4'-Acetoxy-2-chloro-2-(methylthio)acetophenone (**1**) was used as the starting material in the synthesis of the target benzofurans (**4a-e**). The chloride **1** was prepared from 4'-acetoxy-2-(methylthio)acetophenone by the chlorination with *N*-chlorosuccinimide according to the procedure reported by Bohme and Krack in 1977.

The one-pot reaction of *p*-cresol with the chloride **1** in the presence of zinc chloride afforded 5-methyl-3-methylthio-2-(4-acetoxyphenyl)benzofuran (**2a**) in a 63% yield. The structural assignment of **2a** was made based on the spectroscopic evidence. The IR spectrum of **2a** revealed an absorption band for carbonyl (1763 cm^{-1}). The ^{1}H-NMR spectral data for **2a** showed the presence of 16 protons, and the ^{13}C-NMR spectrum displayed signals due to 13 sp^2- and 3 sp^3-hybridized carbon atoms. The mass spectrum (M^+, m/z 312) of **2a** showed the molecular ion peak to be $C_{18}H_{16}O_3S_1$.

The reaction of the 4-substituted phenols with **1** under the same conditions as used for the preparation of **2a** was then examined. The 5-alkyl-3-methylthio-2-(4-acetoxyphenyl) benzofurans (**2b-e**) were obtained in moderate yields. The compounds **2a-e** were hydrolyzed with 2*N* NaOH and methanol solution to give the 5-alkyl-3-methylthio-2-(4-hydroxyphenyl)benzofurans (**3a-e**) in high yields. The compounds **3a-e** were then desulfurized with Raney nickel in ethanol to give the corresponding 5-alkyl-2-(4-hydroxyphenyl)benzofurans (**4a-e**). The preparation of 2-arylbenzofurans involves the coupling of an *o*-halogenphenol with copper (I) arylacetylide (Lutjens and Scammelles,



Scheme 1. Reagents and conditions: i) $ZnCl_2$, CH_2Cl_2, 0°C, 1 h; ii) 2*N*-NaOH, MeOH, rt, 5 h; iii) Raney-Ni (w-2), EtOH reflux, 2 h.



Scheme 2. Synthetic route for compound **7**

1998; Schreiber and Stevenson, 1976), and a reaction of the (2-methoxyphenyl)ethynes with lithium iodide in 2,4,6-trimethylpyridine (Buckle *et al.*, 1985). However, these methods are limited in their versatility by the requisite starting materials.

As shown in Scheme 2, the synthesis of 5-methyl-3-*p*-toluoyl-2-[4-(3-diethylaminopropoxy)phenyl] benzofuran (**7**), which is expected to exhibit the activity of β- amyloid aggregation inhibitor, was designed starting from 5-methyl-2-(4-hydroxyphenyl)benzofuran (**4a**). The *O*-alkylation of compound **4a** with an excess of 1,3-dibromopropane using potassium carbonate as the base gave the bromide **5** in a 62% yield. A Friedel-Crafts acylation of compound **5** with *p*-toluoyl chloride in the presence of $SnCl_4$ afforded the ketone **6** in a 54% yield.

Finally the target compound **7**, was obtained as a high viscous oil by the treatment of compound **6** with an excess of diethylamine in ethanol in a 58% yield. As a β-amyloid aggregation inhibitor, this compound **7** was effective at μM concentrations (IC_{50}=61 μM against 10 μM synthetic β-amyloid 1-42 peptide). Twyman and Allsop reported the synthesis of 3-*p*-toluoyl-2-[4-(3-diethylamino-propoxy)phenyl]benzofuran, as an analog of benzofuran **7**, using an intramolecular Wittig procedure to construct the benzofuran skeleton (Hercouet and Le Corre, 1979). This benzofuran analog has been identified to inhibit the activity for β-amyloid aggregation at IC_{50}=56 μM against 11 μM synthetic β-amyloid 1-40 peptide ((Howlett *et al.*, 1999).

In conclusion, this study developed an efficient route for the synthesis of 2-(4-hydroxyphenyl)benzofurans (**4**) using the reaction of the 4-substituted phenols with the chloride **1** under a Friedel-Crafts reaction condition as the key step. The benzofuran **7**, which was synthesized in three steps starting from compound **4a**, was found to effective as an inhibitor of β-amyloid aggregation. Experiments aimed at obtaining more potent β-amyloid aggregation inhibitors possessing 2-(4-hydroxyphenyl)benzofuran moiety are currently underway.

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