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Synthesis of 5-Chloro-3-[4-(3-diethylaminopropoxy)benzoyl]-2-(4-methoxyphenyl)benzofuran as a β-Amyloid Aggregation Inhibitor

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An efficient synthesis of 5-chloro-3-[4-(3-diethylaminopropoxy)benzoyl]-2-(4-methoxyphenyl)benzofuran (**8**), a potent β-amyloid aggregation inhibitor, is described. 5-Chloro-2-(4-methoxyphenyl)benzofuran (**3**) was obtained by the one-pot synthesis of 4-chlorophenol with ω-(methylsulfinyl)-*p*-methoxyacetophenone (**1**) under Pummerer reaction conditions, and it was followed by the desulfurization of the resultant 5-chloro-3-methylthio-2-(4-methoxyphenyl)benzofuran (**2e**). Acylation of benzofuran **3** with 4-(3-bromopropoxy)benzoyl chloride (**6**) gave the ketone **7**, which was converted into compound **8** by the treatment of diethylamine.

Key words: 5-Chloro-3-[4-(3-diethylaminopropoxy)benzoyl]-2-(4-methoxyphenyl)benzofuran, β-Amyloid aggregation inhibitor, 5-Chloro-2-(4-methoxyphenyl)benzofuran, ω-(Methylsulfinyl)-*p*-methoxyacetophenone, Pummerer reaction conditions, 4-(3-Bromopropoxy)benzoyl chloride

INTRODUCTION

An major pathological feature of many neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, was elucidated due to the aggregation of fibrillar protein (Kakizuka, 1998). Particularly, Hardy and Allsop in 1991, reported that the accumulation of the β-amyloid protein in the brain may be the underlying cause of Alzheimer's disease.

Recently, a number of benzofuran analogues have been studied as potential inhibitors of β-amyloid formation (Howlett *et al.*, 1999), and much attention have been given to the development of more potent inhibitors possessing benzofuran moiety.

In the preceding paper (Choi and Seo, 2001; Kim *et al.*, 2001), we showed that the one-pot reaction of substituted phenols and α-(methylsulfinyl)ketones in the presence of *p*-toluenesulfonic acid provided an excellent method for synthesizing 2-alkylbenzofurans. In this study, our method was applied to the preparation of 2-(4-methoxyphenyl)-benzofurans (**2**), in which ω-(methylsulfinyl)-*p*-methoxyacetophenone (**1**) was employed as an electrophile in place of α-(methylsulfinyl)ketones.

Herein, we report a convenient synthesis of the title compound **8**, 5-chloro-3-[4-(3-diethylaminopropoxy) benzoyl]-2-(4-methoxyphenyl)benzofuran (Howlett *et al.*, 1999), as a potent β-amyloid aggregation inhibitor, starting from 5-chloro-3-methylthio-2-(4-methoxyphenyl) benzofuran (**2e**).

MATERIALS AND METHODS

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

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ω-(Methylsulfinyl)-*p*-methoxyacetophenone (1)
A suspension of sodium hydride (60% mineral oil dispersion; 2.4 g, 60 mmol) in dimethylsulfoxide (40 mL) was heated and stirred at 70-75°C for 40 min under an Ar atmosphere. After cooling to room temperature, tetrahydrofuran (40 mL) was added to the reaction mixture. Then ethyl *p*-methoxybenzoate (4.3 g, 24 mmol) was added to the mixture at 0°C, and then the stirring was continued for 90 min at the room temperature. The reaction mixture was then poured into water (200 mL), which was acidified with 10% hydrochloric acid down to pH 3-4, and was also thoroughly extracted with chloroform (3×40 mL). The combined extracts were washed with water (2×50 mL), dried over anhydrous $MgSO_4$, and evaporated off. The residual solid was recrystallized from ethyl acetate to give **1** (74%, 3.48 g) as a white solid. mp 141-143°C; IR (KBr) 3032, 2933, 2838, 1663 (CO), 1510, 1416, 1321, 1262, 1168, 1026 (SO), cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 3H), 3.89 (s, 3H), 4.33 (d, *J* = 3.51 Hz, 2H), 6.98 (d, *J* = 8.72 Hz, 2H), 7.96 (d, *J* = 8.76 Hz, 2H); MS (EI) m/z 212 (M^+), 195, 166, 134 (100%), 106, 91, 76, 63, 50.

General procedure for the synthesis of 5-alkyl-3-methylthio-2-(4-methoxyphenyl)benzofurans (2)
A solution of **1** (2 mmol, 424 mg), 4-substituted phenol (2 mmol), and anhydrous *p*-toluenesulfonic acid (6 mmol, 1.03 g) in 1,2-dichloroethane (30 mL) was refluxed for 1 h. Then, the mixture was cooled at room temperature, washed with water to remove *p*-toluenesulfonic acid, and dried over anhydrous $MgSO_4$. The solvent was evaporated off, and the residue was purified by column chromatography (hexane/ethyl acetate=4/1) in order to give **2**.

5-Methyl-3-methylthio-2-(4-methoxyphenyl)benzofuran (2a)
Yield 68% (386 mg); mp 70-71°C; IR (KBr) 2911, 2888, 1604, 1498, 1466, 1248, 1180, 1077, 1029 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.49 (s, 3H), 3.88 (s, 3H), 7.02 (d, *J* = 8.96 Hz, 2H), 7.11 (d, *J* = 7.04 Hz, 1H), 7.37 (d, *J* = 8.32 Hz, 1H), 7.48 (s, 1H), 8.24 (d, *J* = 8.96 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.39, 21.42, 55.33, 106.94, 110.65, 113.92, 119.48, 123.17, 125.76, 128.71, 131.32, 132.59, 151.88, 155.64, 160.06; MS (EI) m/z 284 (M^+, 100%), 269, 254, 238, 225, 208, 197, 165, 142, 127, 113, 89, 77, 63, 51.

5-Ethyl-3-methylthio-2-(4-methoxyphenyl)benzofuran (2b)
Yield 66% (394 mg); mp 75-76°C; IR (KBr) 2954, 1604, 1496, 1460, 1252, 1177, 1077, 1028 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.52 Hz, 3H), 2.38 (s, 3H), 2.79 (q, *J* = 7.68 Hz, 2H), 3.88 (s, 3H), 7.02 (d, *J* = 8.96 Hz, 2H), 7.15 (d, *J* = 8.52 Hz, 1H), 7.40 (d, *J* = 8.32 Hz, 1H), 7.51 (s, 1H), 8.24 (d, *J* = 8.96 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.32, 18.41, 28.94, 55.34, 107.06, 110.76, 113.93, 118.28, 123.19, 124.75, 128.71, 131.31, 139.28, 152.01, 155.69, 160.07; MS (EI) m/z 298 (M^+, 100%), 283, 265, 259, 225, 208, 165, 149, 134, 115, 91, 77, 63.

5-*i*-Propyl-3-methylthio-2-(4-methoxyphenyl)benzofuran (2c)
Yield 72% (449 mg); mp 51-52°C; IR (KBr) 2949, 1603, 1459, 1249, 1173, 1026 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 7.04 Hz, 6H), 2.38 (s, 3H), 3.02-3.10 (m, 1H), 3.88 (s, 3H), 7.02 (d, *J* = 8.96 Hz, 2H), 7.19 (d, *J* = 8.44 Hz, 1H), 7.41 (d, *J* = 8.44 Hz, 1H), 7.53 (s, 1H), 8.24 (d, *J* = 8.96 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.41, 24.56, 34.23, 55.34, 107.15, 110.76, 113.93, 116.76, 123.19, 123.39, 128.71, 131.19, 144.02, 152.03, 155.72, 160.06; MS (EI) m/z 312 (M^+, 100%), 297, 255, 227, 211, 178, 165, 148, 133, 115, 92, 77, 63.

5-*t*-Butyl-3-methylthio-2-(4-methoxyphenyl)benzofuran (2d)
Yield 69% (450 mg); mp 60-51°C; IR (KBr) 2955, 1609, 1499, 1467, 1245, 1173, 1020 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.38 (s, 3H), 3.88 (s, 3H), 7.02 (d, *J* = 8.32 Hz, 2H), 7.36-7.44 (m, 2H), 7.68 (s, 1H), 8.24 (d, *J* = 8.44 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.44, 31.88, 34.83, 55.35, 107.34, 110.45, 113.93, 115.76, 122.50, 123.22, 128.71, 130.82, 146.30, 151.70, 155.72, 160.05; MS (EI) m/z 326 (M^+), 280 (100%), 265, 250, 237, 209, 194, 181, 165, 152, 135, 118, 97, 76, 63.

5-Chloro-3-methylthio-2-(4-methoxyphenyl)benzofuran (2e)
Yield 48% (293 mg); mp 104-105°C; IR (KBr) 3072, 2911, 1604, 1494, 1445, 1252, 1172, 1035 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.88 (s, 3H), 7.02 (d, *J* = 8.96 Hz, 2H), 7.26 (s, 1H), 7.40 (s, *J* = 8.60 Hz, 1H), 7.65 (d, *J* = 2.21 Hz, 1H), 8.25 (d, *J* = 8.96 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.37, 55.36, 106.88, 112.11, 114.03, 119.33, 122.52, 124.67, 128.85, 132.88, 146.33, 151.81, 157.02, 160.45; MS (EI) m/z 306 (M+2), 304 (M^+, 100%), 289, 254, 239, 218, 186, 152, 139, 113, 87, 63.

5-Chloro-2-(4-methoxyphenyl)benzofuran (3)
Compound **2e** (900 mg, 2.97 mmol) was heated under the reflux in ethanol (50 mL) containing Raney nickel (W-2, 4 g) for 2 h. The Raney nickel was removed by filtration, and the solvent was allowed to evaporate. The residual solid was recrystallized from ethanol to give **3** (662 mg, 86%). mp 166-167°C; IR (KBr) 2957, 1608, 1500, 1448, 1254, 1174, 1032 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.82 (s, 1H), 6.98 (d, *J* = 8.84 Hz, 2H), 7.21 (dd, *J*

= 6.72 and J = 2.16 Hz, 1H), 7.40 (d, J = 8.60 Hz, 1H), 7.51 (d, J = 2.12 Hz, 1H), 7.80 (d, J = 8.88 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 55.38, 111.88, 114.32, 120.07, 120.55, 122.79, 123.81, 126.57, 128.36, 130.88, 153.07, 157.55, 160.31; MS (EI) m/z 260 (M+2), 258 (M^+, 100%), 243, 215, 180, 163, 129, 118, 87, 75, 63, 51.

Methyl 4-(3-bromopropoxy)benzoate (4)

A mixture of methyl *p*-hydroxybenzoate (2.28 g, 15 mmol), 1,3-dibromopropane (4.85 g, 24 mmol), and potassium carbonate (2.48 g, 18 mmol) in acetone (50 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 (benzene) to give **4** (2.74 g, 67%) as a colorless oil. IR (neat) 2949, 1716 (CO), 1605, 1509, 1435, 1256, 1171, 1110, 1027 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.30-2.37 (m, 2H), 3.60 (t, J = 6.48 Hz, 2H), 3.88 (s, 3H), 4.16 (t, J = 5.92 Hz, 2H), 6.92 (d, J = 6.96 Hz, 2H), 7.99 (d, J = 6.72 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.66, 32.16, 51.85, 65.45, 114.07, 122.84, 131.60, 162.39, 166.76; MS (EI) m/z 274 (M+2), 272 (M^+), 241, 193, 152, 135, 121 (100%), 103, 93, 65.

4-(3-Bromopropoxy)benzoic acid (5)

Compound **4** (2.18 g, 8.0 mmol) was added to a solution of sodium hydroxide (1.92 g, 48 mmol) in water (50 mL), and the mixture was stirred for 10 h at room temperature. Then, 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 $MgSO_4$. The solvent was allowed to evaporate, and the residue was recrystallized from isopropanol to give **5** (1.76 g, 85%) in the form of a white solid. mp 155-156°C; IR (KBr) 2943 (OH), 1680 (CO), 1604, 1509, 1428, 1299, 1252, 1169, 1032 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.32-2.39 (m, 2H), 3.62 (t, J = 6.20 Hz, 2H), 4.19 (t, J = 5.92 Hz, 2H), 6.96 (d, J = 9.12 Hz, 2H), 8.07 (d, J = 9.12 Hz, 2H), 10.8 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.62, 32.13, 65.54, 114.22, 121.86, 132.39, 163.14, 171.56 ; MS (EI) *m/z* 260 (M+2), 258 (M^+), 179, 151, 138 (100%), 121, 93, 81, 65.

4-(3-Bromopropoxy)benzoyl chloride (6)

N,N-Dimethylformamide (1 drop) was added to a solution of **5** (887 mg, 3.2 mmol) in thionyl chloride (2 mL), and the mixture was refluxed for 90 min. The excess thionyl chloride was removed under reduced pressure to give **6** (782 mg). **6** was used for the next step in its crude form without further purification. IR (neat) 2947, 1740 (CO), 1601, 1507, 1428, 1261, 1218, 1166, 1029 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.15-2.56 (m, 2H), 3.60 (t, J = 5.82 Hz, 2H), 4.22 (t, J = 5.88 Hz, 2H), 6.98 (d, J = 8.82 Hz, 2H), 8.09 (d, J = 8.82 Hz, 2H).

5-Chloro-3-[4-(3-bromopropoxy)benzoyl]-2-(4-methoxyphenyl)benzofuran (7)

Stannic chloride (782 mg, 3.0 mmol) was added to a stirred solution of **3** (646 mg, 2.5 mmol) and 4-(3-bromopropoxy)benzoyl chloride **6** (782 mg, 3.0 mmol) in benzene (20 mL) at room temperature under an Ar 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 $MgSO_4$, and was concentrated under the reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate=4:1) to give **7** (737 mg, 59%) as a high viscous oil. IR (neat) 2942, 1643 (CO), 1602, 1504, 1447, 1367, 1307, 1259, 1173, 1108, 1028 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.30-2.36 (m, 2H), 3.59 (t, J = 6.52 Hz, 2H), 3.80 (s, 3H), 4.14 (t, J = 5.84 Hz, 2H), 6.83-6.86 (m, 4H), 7.22-7.33 (m, 2H), 7.46 (d, J = 6.16 Hz, 1H), 7.63 (d, J = 9.04 Hz, 2H), 7.84 (d, J = 8.88 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.61, 32.09, 55.34, 65.51, 110.01, 112.00, 113.97, 114.29, 120.67, 121.12, 123.53, 124.79, 125.04, 129.27, 129.71, 129.81, 132.28, 151.92, 153.52, 160.67, 190.28; MS (EI) m/z 499 (M^+), 454, 420 (100%), 403, 384, 343, 315, 251, 197, 152, 121, 93, 71, 57.

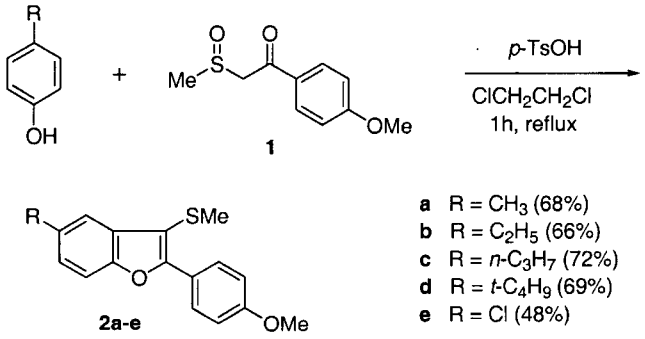
5-Chloro-3-[4-(3-diethylaminopropoxy)benzoyl]-2-(4-methoxyphenyl)benzofuran (8)

A mixture of **7** (700 mg, 1.40 mmol) and diethylamine (256 mg, 3.5 mmol) in ethanol (20 mL) was refluxed for 20 h. The reaction mixture was concentrated under the reduced pressure, and was quenched by the addition of water (30 mL). The aqueous solution was adjusted to a pH of 10 with 10% potassium hydroxide solution, and was extracted with ethyl acetate (20 mL×2). The combined extracts were dried over anhydrous $MgSO_4$, and then, evaporated. The residue was purified by column chromatography (methanol) to give **8** (461 mg, 67%) as a thick honey colored oil. IR (neat) 2966, 1642 (CO), 1602, 1505, 1449, 1369, 1305, 1254, 1173, 1103, 1031 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.20 Hz, 6H), 1.89-1.97 (m, 2H), 2,53 (q, J = 7.16 Hz, 4H), 2.59 (t, J = 7.31 Hz, 2H), 3.80 (s, 3H), 4.05 (t, J = 6.32 Hz, 2H), 6.82-6.85 (m, 4H), 7.21-7.32 (m, 2H), 7.46 (d, J = 5.80 Hz, 1H), 7.65 (d, J = 8.88 Hz, 2H), 7.83 (d, J = 8.88 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.76, 26.93, 47.02, 49.19, 55.31, 66.60, 110.99, 111.98, 113.95, 1114.35, 120.69, 121.14, 123.49, 124.75, 124.99, 129.68, 129.79, 132.25, 132.28, 151.91, 153.53, 163.49, 190.33; MS (EI) m/z 493 (M+2), 491 (M^+), 418 (100%), 401, 377, 361, 314, 285, 271, 243, 229, 161, 121, 105, 77, 63, 51.

RESULTS AND DISCUSSION

ω-(Methylsulfinyl)-*p*-methoxyacetophenone (**1**) was prepared from the reaction of ethyl *p*-methoxybenzoate with methylsulfinyl carbanion using the procedure reported by Corey and Chaykovsky in 1965. On the basis of our synthetic method for the 2-alkylbenzofuran ring using α-(methylsulfinyl)ketones under Pummerer reaction conditions (Choi and Seo, 2001; Kim *et al.*, 2001), we attempted the synthesis of 2-(4-methoxyphenyl)benzofurans **2** as illustrated in Scheme 1. Thus, the treatment of equimolar amounts of 4-alkylphenols and sulfoxide **1** in 1,2-dichloroethane, with three equivalents of anhydrous *p*-toluenesulfonic acid under reflux, gave good yields of the adducts **2a-d**.

The reaction of 4-chlorophenol with the sulfoxide **1** furnished a 48% yield of 5-chloro-3-methylthio-2-(4-methoxyphenyl)benzofuran (**2e**) under the same conditions.



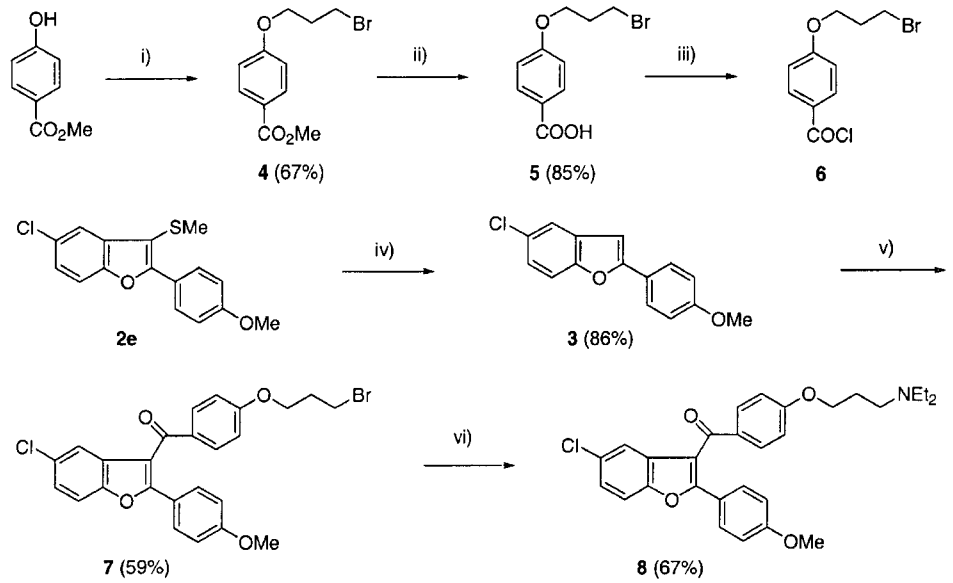
Scheme 1. Synthesis of 5-alkyl-e-methylthio-2-(4-methoxyphenyl)benzofurans (**2a-e**)

The structural assignment of **2e** was made on the basis of its spectroscopic evidence. The ^{1}H-NMR spectral data showed the presence of two methyl protons and seven aromatic protons. The ^{13}C-NMR spectrum displayed peaks due to 12 sp^2- and 2 sp^3-hybridized carbon atoms. The mass spectrum showed the molecular ion peak [M^+] at m/z 304 and [M+2] at m/z 306, respectively. The compound **2e** could easily be desulfurizied into the corresponding 5-chloro-2-(4-methoxyphenyl)benzofuran (**3**) by heating it with Raney nickel in ethanol of 86% yield.

In the synthetic route leading to 3-*p*-toluoyl-2-[4-(3-diethylaminopropoxy)phenyl]benzofuran, a β-amyloid aggregation inhibitor, Twyman and Allsop used 2-(4-methoxyphenyl)benzofuran obtained by an intrarnolecular Wittig procedure (Hercouet and Corre, 1979). However, the above method is limited in its versatility due to Wittig reagents, such as *O*-hydroxybenzyl triphenylphosphonium bromide, the requisite starting materials.

As shown in Scheme 2, we prepared 4-(3-bromopropoxy)benzoyl chloride (**6**) starting from methyl *p*-hydroxybenzoate. The *O*-alkylation of methyl *p*-hydroxybenzoate, with excess 1,3-dibromopropane and also using potassium carbonate as a base, gave the bromide **4** a yield of 67%. Compound **4** was hydrolyzed with sodium hydroxide solution to give acid **5** a yield of 85%. Acid chloride **6** was obtained from the treatment of excess thionyl chloride with acid **5**.

Friedel-Crafts acylation of benzofuran **3** with 4-(3-bromopropoxy)benzoyl chloride (**6**) in benzene, using stannic chloride as the Lewis acid, afforded the benzofuran derivative **7** with 59% yield. Finally, the treatment of compound **7** with an excess of diethylamine in ethanol,



Scheme 2. Reagents and conditions: i) 1,3-dibromopropane, KOH, acetone, reflux, 20 h; ii) NaOH, H_2O, 10 h, rt; iii) $SOCl_2$, 15 h; iv) Raney nickel, EtOH, reflux, 2 h; v) compound 6, benzene, $SnCl_4$, 24 h; vi) diethylamine, EtOH, reflux, 20 h.

afforded the target compound, 5-chloro-3-[4-(3-diethylaminopropoxy)benzoyl]-2-(4-methoxyphenyl)benzofuran (**8**), 67% yield, which appeared as a thick honey colored oil. This compound was effective at μm concentrations (IC50 =28 μm against 11 μm synthetic β-amyloid 1-40 peptide) (Howlett *et al.*, 1999).

In conclusion, we accomplished the efficient synthesis of a potent β-amyloid aggregation inhibitor, 5-chloro-3-[4-(3-diethylaminopropoxy)benzoyl]-2-(4-methoxyphenyl)-benzofuran (**8**). The key step involved the one-pot reaction of 4-chlorophenol with ω-(methylsulfinyl)-*p*-methoxyacetophenone (**1**) in the presence of *p*-toluenesulfonic acid to form 5-chloro-3-methylthio-2-(4-methoxyphenyl)benzofuran (**2e**). We are currently devising a series of 2-(4-methoxyphenyl)benzofuran derivatives that will aid in the development of more potent β-amyloid aggregation inhibitors.

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