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단 신

치환페놀류로부터 2-(멀티메톡시페닐)벤조[b]푸란 유도체의 합성 및 응용

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Synthesis of 2-(Multimethoxyphenyl)benzo[b]furan Derivatives from Substituted Phenols and Application

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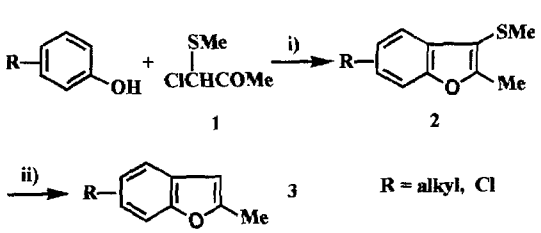
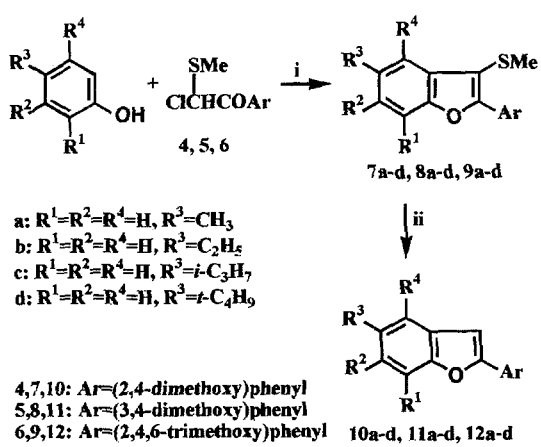
In the preceding paper,[1] we reported that the one step reaction of substituted phenols with α-chloro-α-(methylthio)acetone (**1**) in the presence of Lewis acid provided a convenient method for synthesizing 2-methylbenzo[b]furan derivatives **3** through reductive desulfurization of the resultant products **2** (*Scheme* 1).

We became interested in reports concerning the synthesis and biological activity of natural products having a benzo[b]furan moiety. Among the constituents isolated from *Myroxylon balsamum*,[2] *Sophora tomentosa*,[3] *Krameria ramosissima*,[4] and *Zanthoxylum ailanthoides*,[5] its closely related natural products possess a benzo[b]furan skeleton bearing the (di, tri, and multi methoxy)phenyl groups in the 2-position. As part of our basic research on the construction of 2-(multimethoxyphenyl)benzo[b]furan ring, the reactions of substituted phenols with the chlorides **4-6** in the presence of Lewis acid were attempted. Concomitantly, our method was applied to the synthesis of a demethoxyhomoegonol **15**, which is an analogue of naturally occurring arylbenzofuranpropanols.[6]

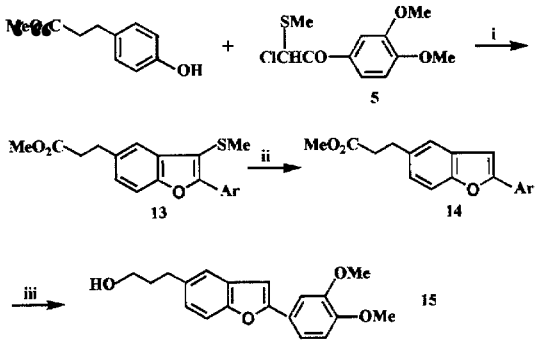


Scheme 1.

As shown in *Scheme* 2, the treatment of substituted phenols with **4** and **5** in the presence of $ZnCl_2$ afforded the corresponding 2-aryl 3-(methylthio)benzo[b]furans **7** and **8** in the range of 75-80% yields, respectively. The compounds **7** and **8** were easily desulfurized by heating with Raney nickel in ethanol to give the corresponding 2-



Scheme 2. Reagents and conditions: (i) $ZnCl_2$, CH_2Cl_2, -5°C, 1h; (ii) Raney-nickel, EtOH, 60-65°C, 1h.



Scheme 3.

arylbenzo[b]furans **10** and **11** in high yields.

Similarly, the reaction of substituted phenols and the chloride **6** under the same conditions such as preparation for **7** gave the corresponding 2-(2',4',6'-trimethoxyphenyl)-3-(methylthio)benzo[b]furans **9** in the range of 61-68% yields. In this case, the low yields in comparison with the reaction of the chlorides **4-5** are attributed to the steric hindrance of two methoxy groups in the C_2- and C_6-positions on the chloride **6**. The desulfurization of **9** with Raney nickel in ethanol afforded the corresponding 2-(2',4',6'-trimethoxyphenyl)benzo[b]furans **12** in high yields.

Finally, we applied this reaction to the synthesis of a demethoxyhomoegonol **15** having 3,4-dimethoxyphenyl group in the 2-position (*Scheme* 3). The reaction of 3-(4-hydroxyphenyl)propionate with **5** in the presence of zinc chloride afforded 2-aryl-3-(methylthio)benzo[b]furan **13** in 65% yield. The desulfurization of **13** with Raney nickel in ethanol gave 2-arylbenzo[b]furan **14** in 82% yield. The desired compound, a demethoxyhomoegonol **15** was obtained from reduction of the methyl ester **14** with excess $LiAlH_4$ in 93% yield.

Of the several syntheses available for the construction of the benzo[b]furan nucleus, a relatively general method involved the coupling of substituted ortho-halophenols with cuprous arylacetylides and concommitant cyclization.[7] However, the above method utilizing stoichiometric amounts of copper proved difficult to scale up.

In conclusion, we have described a facile synthesis of 2-(multimethoxyphenyl)benzo[b]furans **10-12** by two steps: i) benzo[b]furan ring formation from one-pot reaction of substituted phenols with the chlorides **4-6** under Friedel-Crafts reaction conditions; ii) the reductive desulfurization of the resultant products **7-9**. The new synthesis of a demethoxyhomoegonol **15**, an analogue of naturally occurring arylbenzofuranpropanols, could be accomplished by three steps starting from methyl 3-(4-hydroxyphenyl) propionate and the chloride **5**.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi R-1500 FT NMR (60 MHz) spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FT/IR-300E spectrometer. Mass spectra were determined at 70 eV with a Hewlett Packard 5970 GC/MS system by the electron impact (EI) method. Silica gel 60 (70-230 mesh, E. Merck) was used for column chromatography.

General procedure for the synthesis of 2-(2',4'-dimethoxyphenyl)-3-(methylthio)benzo[b]furans (7). To a solution of **4** (495 mg, 1.9 mmol) and a substituted phenol (1.9 mmol) in CH_2Cl_2 (15 mL) was added $ZnCl_2$ (273 mg, 2.0 mmol) at -5°C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 1h. The reaction was quenched by the addition of water and then extracted with CH_2Cl_2 (10 mL). The combined extracts was dried over anhydrous $MgSO_4$, concentrated in vacuo, and the resulting concentrate was purified by column chromatography (benzene) to give **7**. **7a:** Yield 78%; mp 160-161°C; ^{1}H NMR ($CDCl_3$) δ2.49(s, 3H), 3.10(s, 3H), 3.82(s, 3H), 3.87(s, 3H), 6.30-8.02(m, 6H); IR (KBr) 2922, 1619, 1580, 1465, 1209, 1163 cm^{-1}; MS m/z 314(M^+), 299, 268, 253, 225, 165, 151. **7b:** Yield 76%; mp 121-122°C; ^{1}H NMR ($CDCl_3$) δ1.31(t, 3H, J=7.6Hz), 2.31(s, 3H), 2.80(q, 2H, J=7.6Hz), 3.84(s, 3H), 3.88(s, 3H), 6.41-7.68(m, 6H); IR (KBr) 2962, 2927, 1615, 1582, 1501, 1470, 1285, 1160, 1064 cm^{-1}; MS m/z 328(M^+), 313, 279, 251, 224, 191, 165, 147. **7c:** liquid; Yield 79%; ^{1}H NMR ($CDCl_3$) δ 1.33(d, 6H, J=7.0Hz), 2.31(s, 3H), 2.64-3.48(m, 1H), 3.83(s, 3H), 3.87(s, 3H), 6.36-7.73(m, 6H); IR (neat) 2959, 1615, 1582, 1501, 1477, 1287, 1160, 1036 cm^{-1}; MS m/z 342(M^+), 327, 296, 284, 265, 179, 163, 140. **7d:** liquid; Yield 75%; ^{1}H NMR ($CDCl_3$) δ1.42(s, 9H), 2.30(s, 3H), 3.82(s, 3H), 3.87(s, 3H), 6.32-7.80(m, 6H); IR (neat)

2959, 1617, 1581, 1459, 1286, 1210, 1160, 1035 cm^{-1}; MS m/z 356(M^+), 341, 310, 279, 251, 170, 149.

General procedure for the synthesis of 2-(3',4'-dimethoxyphenyl)-3-(methylthio)benzo[b]furans (8). By the same procedure for the preparation of **7**, compounds **8** were obtained from **5** (495 mg, 1.9 mmol), a substituted phenol (1.9 mmol) and $ZnCl_2$ (273 mg, 2.0 mmol). **8a:** Yield 75%; mp 114-116°C; ^1H NMR ($CDCl_3$) δ2.37(s, 3H), 2.48(s, 3H), 3.94(s, 3H), 3.98(s, 3H), 6.75-8.16(m, 6H); IR (KBr) 2911, 2833, 1600, 1511, 1466, 1277, 1243, 1155 cm^{-1}; MS m/z 314(M^+), 299, 284, 268, 253, 225, 157. **8b:** Yield 80%; mp 79-80°C; ^1H NMR ($CDCl_3$) δ1.32(t, 3H, J=7.6Hz), 2.38(s, 3H), 2.80(q, 2H, J=7.6Hz), 3.96(s, 3H), 3.99(s, 3H), 6.81-8.15(m, 6H); IR (KBr) 2955, 2911, 1511, 1466, 1288, 1255, 1155 cm^{-1}; MS m/z 328(M^+), 313, 282, 267, 164, 149. **8c:** Yield 74%; mp 101-102°C; ^1H NMR ($CDCl_3$) δ1.34(d, 6H, J=7.0Hz), 2.38(s, 3H), 2.73-3.48(m, 1H), 3.96(s, 3H), 3.99(s, 3H), 6.80-8.15(m, 6H); IR (KBr) 2944, 2867, 1499, 1466, 1288, 1255, 1144 cm^{-1}; MS m/z 342(M^+), 327, 296, 281, 254, 163. **8d:** Yield 76%; mp 111-113°C; ^1H NMR ($CDCl_3$) δ1.42(s, 9H), 2.38(s, 3H), 3.94(s, 3H), 3.99(s, 3H), 6.80-8.10(m, 6H); IR (KBr) 2955, 2911, 1511, 1466, 1255, 1221, 1155 cm^{-1}; MS m/z 356(M^+), 341, 310, 295, 270, 254, 170, 156.

General procedure for the synthesis of 2-(2',4',6'-trimethoxyphenyl)-3-(methylthio)benzo[b]furans (9). By the same procedure for the preparation of **7**, compounds **9** were obtained from **6** (551 mg, 1.9 mmol), a substituted phenol (1.9 mmol) and $ZnCl_2$ (273 mg, 2.0 mmol). **9a:** Yield 66%; mp 137-139°C; ^1H NMR ($CDCl_3$) δ2.29(s, 3H), 2.49(s, 3H), 3.75(s, 6H), 3.87(s, 3H), 6.21(s, 2H), 7.12-7.63(m, 3H); IR (KBr) 2935, 2837, 1621, 1584, 1464, 1412, 1226, 1207, 1130 cm^{-1}; MS m/z 344(M^+), 296, 283, 267, 240, 221, 151. **9b:** Yield 68%; mp 135-137°C; ^1H NMR ($CDCl_3$) δ1.31(t, 3H, J=7.0Hz), 2.30(s, 3H), 2.72(q, 2H, J=7.6Hz), 3.74(s, 6H), 3.87(s, 3H), 6.21(s, 2H), 6.93-7.69(m, 3H); IR (KBr) 2967, 2921, 1622, 1582, 1459, 1437, 1205, 1154 cm^{-1}; MS m/z 358(M^+), 310, 297, 281, 254, 221, 179, 165. 9c: Yield 63%; mp 119-120°C; ^1H NMR ($CDCl_3$) δ1.33(d, 6H, J=7.0Hz), 2.28(s, 3H), 2.67-3.50(m, 1H), 3.74(s, 6H), 3.87(s, 3H), 6.21(s, 2H), 6.94-7.68(m, 3H); IR (KBr) 2963, 1623, 1583, 1458, 1227, 1205, 1155, 1130 cm^{-1}; MS m/z 372(M^+), 357, 324, 311, 221, 179. **9d:** Yield 61%; mp 74-75°C; ^1H NMR ($CDCl_3$) δ1.42(s, 9H), 2.30(s, 3H), 3.74(s, 6H), 3.87(s, 3H), 6.21(s, 2H), 7.10-7.89(m, 3H); IR (KBr) 2958, 1618, 1585, 1459, 1414, 1227, 1158, 1129 cm^{-1}; MS m/z 386(M^+), 371, 338, 324, 281, 221, 193, 165.

General procedure for the synthesis of 2-(2',4'-dimethoxyphenyl) benzo[b]furans (10). A solution of **7** (200-400 mg) and Raney nickel (W-2, 2-4 g) in EtOH (20 mL) was heated at 60-65°C for 1h. The Raney nickel was removed by filtration and the solvent was evaporated off. The residue was chromatographed with benzene as an eluent to give **10**. **10a:** Yield 92%; mp 105-107°C; ^1H NMR ($CDCl_3$) δ2.43(s, 3H), 3.85(s, 3H), 3.96(s, 3H), 6.38-8.14(m, 7H); IR (KBr) 2936, 1607, 1502, 1296, 1257, 1210, 1160 cm^{-1}; MS m/z 268(M^+), 253, 225, 210, 181, 165, 148, 134. **10b:** Yield 87%; mp 84-85°C; ^1H NMR ($CDCl_3$) δ1.28(t, 3H, J=7.6Hz), 2.74(q, 2H, J=7.6Hz), 3.86(s, 3H), 3.97(s, 3H), 6.32-8.23(m, 7H); IR (KBr) 2959, 2930, 1607, 1505, 1466, 1290, 1267, 1209 cm^{-1}; MS m/z 282(M^+), 267, 239, 209, 181, 148, 133. **10c:** Yield 95%; mp 80-81°C; ^1H NMR ($CDCl_3$) δ1.29(t, 3H, J=6.5HZ), 2.58-3.42(m, 1H), 3.85(s, 3H), 3.96(s, 3H), 6.25-8.23(m, 7H); IR (KBr) 2952, 2833, 1608, 1504, 1456, 1289, 1209, 1157 cm^{-1}; MS m/z 296(M^+), 281, 266, 223, 165, 140, 117. **10d:** Yield 86%; mp 87-88°C; ^1H NMR ($CDCl^3$) δ1.38(s, 9H), 3.86(s, 3H), 3.96(s, 3H), 6.37-8.17(m, 7H); IR (KBr) 2956, 2359, 1615, 1505, 1456, 1289, 1213, 1160 cm^{-1}; MS m/z 310(M^+), 295, 280, 237, 209, 165, 147, 133.

General procedure for the synthesis of 2-(3',4'-dimethoxyphenyl)benzo[b]furans (11). By the same procedure for the preparation of **10**, compounds **11** were obtained from **8** (200-400 mg) and Raney nickel (2-4 g). The residue was chromatographed with benzene as an eluent to give **11**. **11a:** Yield 83%; mp 124-126°C; ^1H NMR ($CDCl^3$) δ2.43(s, 3H), 3.92(s, 3H), 3.98(s, 3H), 6.60-7.71(m, 7H); IR (KBr) 2966, 2932, 1509, 1470, 1255, 228, 1168, 1142 cm^{-1}; MS m/z 268(M^+), 253, 225, 197, 181, 152, 134. **11b:** Yield 93%; mp 104-106°C; ^1H NMR ($CDCl_3$) δ1.28(t, 3H, J=7.6Hz), 2.74(q, 2H, J=7.6Hz), 3.92(s, 3H), 3.98(s, 3H), 6.64-7.71(m, 7H); IR (KBr) 2961, 1508, 1466, 1249, 1229, 1142, 1022 cm^{-1}; MS m/z 282(M^+), 265, 239, 209, 181, 165, 152, 133, 112. **11c:** Yield 95%; mp 117-119°C; ^1H NMR ($CDCl_3$) δ 1.31(t, 3H, J=7.0HZ), 2.62-3.48(m, 1H), 3.93 (s, 3H), 3.78(s,

3H), 6.61-7.78(m, 7H); IR (KBr) 2955, 1509, 1473, 1268, 1253, 1140, 1019 cm^{-1}; MS m/z 296(M^+), 281, 253, 223, 183, 165, 140. **11d:** Yield 91%; mp 139-141°C; ^1H NMR ($CDCl^3$) δ1.39(s, 9H), 3.93(s, 3H), 3.98 (s, 3H), 6.68-7.72(m, 7H); IR (KBr) 2956, 1509, 1465, 1271, 1256, 1138, 1023 cm^{-1}; MS m/z 310(M^+), 295, 267, 237, 209, 165, 147, 112.

General procedure for the synthesis of 2-(2',4',6'-trimethoxyphenyl)benzo[b]furans (12). By the same procedure for the preparation of **10**, compounds **12** were obtained from **9** (200-400 mg) and Raney nickel (2-4 g). The residue was chromatographed with benzene as an eluent to give **12. 12a:** Yield 83%; mp 110-112°C; ^1H NMR ($CDCl^3$) δ2.44(s,3H), 3.79(s, 6H), 3.87(s, 3H), 6.21(s, 2H), 6.59-7.55(m, 4H); IR (KBr) 2957, 2934, 1613, 1579, 1468, 1411, 1226, 1155, 1131 cm^{-1}; MS m/z 298(M^+), 283, 255, 240, 225, 178, 149. **12b:** Yield 90%; mp 82-83°C; ^1H NMR ($CDCl_3$) δ1.27(t, 3H, J=7.1Hz), 2.74(q, 2H, J=7,6Hz), 3.78(s, 6H), 3.86(s, 3H), 6.21(s, 2H), 6.52-7.63(m, 4H); IR (KBr) 2961, 2934, 1629, 1585, 1465, 1414, 1227, 1133 cm^{-1}; MS m/z 312(M^+), 297, 269, 239, 178, 156. **12c:** Yield 82%; mp 68-69°C; ^1H NMR ($CDCl_3$) δ1.30(d, 6H, J=7.0Hz), 2.58-3.45(m, 1H), 3.78(s, 6H), 3.86(s, 3H), 6.21(s, 2H), 6.54-7.73(m, 4H); IR (KBr) 2961, 1613, 1585, 1473, 1227, 1204, 1157, 1126 cm^{-1}; MS m/z 326(M^+), 311, 283, 253, 178, 155. **12d:** liquid; Yield 86%; ^1H NMR ($CDCl_3$) δ1.40(s, 9H), 3.76(s, 3H), 3.86(s, 3H), 6.21(s, 2H), 7.16-7.64(m, 4H); IR (neat) 2963, 1617, 1587, 1466, 1226, 1159, 1129 cm^{-1}; MS m/z 340(M^+), 325, 297, 265, 195, 162, 131.

Methyl 3-[2-(3,4-dimethoxyphenyl)-3-methylthiobenzofuran-5-yl]propionate (13). By the same procedure for the preparation of **7**, compound **13** was obtained from **5** (990 mg, 3.8 mmol), methyl 3-(4-hydroxyphenyl) propionate (685 mg, 3.8 mmol) and $ZnCl_2$ (546 mg, 4.0 mmol). The residue was purified by column chromatography (hexane/ethyl acetate=1/1) to give **13**(953 mg, 65%) as a white solid. mp 96-96°C; ^1H NMR ($CDCl_3$) δ2.37(s, 3H), 2.31-3.47(m, 4H), 3.69(s, 3H), 3.96(s, 3H), 3.99(s, 3H), 6.67-8.14(m, 6H); IR (KBr) 3000, 2954, 1732, 1465, 1247, 1232, 1174, 1028 cm^{-1}; MS m/z 386(M^+), 340, 297, 280, 165.

Methyl 3-[2-(3,4-dimethoxyphenyl)benzofuran-5-yl] propionate (14). By the same procedure for the preparation of **10**, compound **14** was obtained from **13** (656 mg, 1.7 mmol)) and Raney nickel (6.5 g). The residual solid was recrystallized from methanol to give **14** (474 mg, 82%) as a white solid. mp 113-115°C (lit.[6] 113-115°C); ^1H NMR ($CDCl_3$) δ2.38-3.37(m, 4H), 3.67(s, 3H), 3. 93(s, 3H), 3.98(s, 3H), 6.67-7.68(m, 7H); IR (KBr) 3003, 2954, 1732, 1510, 1463, 1253, 1143 cm^{-1}.

5-(3-Hydroxypropyl)-2-(3,4-dimethoxyphenyl)benzofurans (15). A solution of **14** (350 mg, 1.03 mmol) in THF (10 mL) was added to stirred suspension of $LiAlH_4$ (500 mg, 13 mmol) in THF (10 mL) at 0°C under N_2 atmosphere. The mixture was allowed to come to room temperature and stirred for 5h. The reaction was quenched by the addition of water (20 mL) and 10% H_2SO_4 (20 mL). The mixture was extracted with diethyl ether (30 mL×2), the extracts were dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The residual solid was recrystallized from aqueous methanol to give 15 (299 mg, 93%) as a white solid. mp 109-111°C (lit.[6] 108-110°C); ^1H NMR ($CDCl_3$) δ1.54(s, 1H), 1.52-2.33 (m, 2H), 2.82(t. 2H, J=6.5 Hz), 3.70(t, 2H, J=6.5Hz), 3.93(s, 3H), 3.98(s, 3H), 6.54-7.53(m, 7H); IR (KBr) 3343, 3255, 2921, 2844, 1510, 1266, 1144 cm^{-1}.

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