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단 신

오메가-(메틸술피닐)아세토페논류를 이용한 2-아릴벤조푸란 유도체의 합성

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Synthesis of 2-Arylbenzofuran Derivatives Using ω-(Methylsulfinyl)acetophenones

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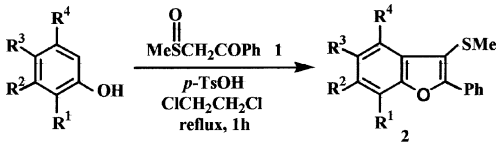
A series of benzofuran ring system bearing various substituents at the C-2 position is widely distributed in nature and has recently become of interest in biological properties. There are well known natural products having related benzofuran ring structures, particularly those isolated from *Machilus glaucescens*,[1] *Ophryosporus charua*,[2] *Ophryosporus lorentzii*,[3] *Krameria ramosissima*,[4] and *Zanthoxylum ailanthoidol*.[5]

For the carbon-carbon bond formation using 1-acyl-1-thiocarbocations, we found that 2-methyl- and arylbenzofurans were easily prepared by the one-pot reaction of substituted phenols with 1-acyl-1-chlorosulfides in the presence of a Lewis acid.[6] Also a facile one-pot procedure was developed, which offers 2-alkylbenzofurans from substituted phenols using α-acylsulfoxides in the presence of *p*-toluenesulfonic acid.[7]

In this paper, we report a new route for synthesizing of 2-arylbenzofuran derivatives from substituted phenols with α-acylsulfoxides (**1**,**3**,**4**) under Pummerer reaction conditions.

As preparation of the starting materials, ω-(methylsulfinyl)acetophenone (**1**) was obtained from the oxidation of 2-(methylthio)acetophenone with sodium metaperiodate in aqueous methanol in 80% yield. The reactions of ethyl *p*-toluate and ethyl *p*-chlorobenzoate with methylsulfinyl carbanion[8] afforded ω-methylsulfinyl-*p*-methylacetophenone (**3**) and ω-methylsulfinyl-*p*-chloroacetophenone (**4**) in 74% and 79% yields, respectively.

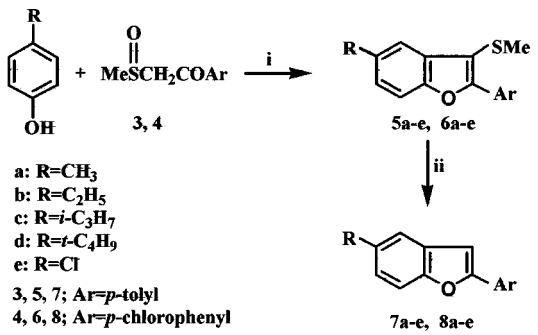
On the basis of our synthetic method[7] for 2-methylbenzofurans using α-(methylsulfinyl)acetone under Pummerer reaction conditions, we first attempted the synthesis of 2-phenylbenzofurans **2** as illustrated in *Scheme* 1. Thus, treatment of equimolar amounts of substituted phenols and the sulfoxide **1** in 1,2-dichloroethane with three equivalents of anhydrous *p*-toluenesulfonic acid under reflux gave the compounds **2a-f** in moderate yields. The spectroscopic data (mp, IR, and ^{1}H NMR) were in good agreements with those reported by our pre-



2a: 80% 2d: 83%
2b: 79% 2e: 78%
2c: 82% 2f: 53%

a: R^1=R^2=R^4=H, R^3=CH_3 d: R^1=R^2=R^4=H, R^3=*t*-C_4H_9
b: R^1=R^2=R^4=H, R^3=C_2H_5 e: R^1=R^3=CH_3, R^2=R^4=H
c: R^1=R^2=R^4=H, R^3=*i*-C_3H_7 f: R^1=R^3=H, R^2=R^4=CH_3

Scheme 1



Scheme 2. Reagents and conditions: (i) *p*-TsOH, $ClCH_2CH_2Cl$, reflux, 1 h; (ii) Raney-Ni (W-2), EtOH, 60-65 °C, 1 h.

vious work[6h] on the synthesis of 2-methylthio-2-phenylbenzofurans under Friedel-Crafts reaction conditions. The procedure for desulfurization of the adducts **2a-f** by heating with Raney nickel in ethanol was reported previously.[6b]

Secondly, we applied the above method to syntheses of 3-methylthio-2-(*p*-tolyl)benzofurans (**5**) and 3-methylthio-2-(*p*-chlorophenyl)benzofurans (**6**), in which the sulfoxides **3** and **4** are employed as electrophiles in place of **1**. The Pummerer reactions of *para*-substituted phenols with **3** and **4** were carried out as shown in *Scheme* 2.

The treatment of equimolar amounts of *para*-substituted phenols and the sulfoxide **3** in the presence of three equivalents of *p*-toluenesulfonic acid afforded the compounds **5a-e** in satisfactory yields. Also the compounds **6a-e** were obtained from the reactions of *para*-substituted phenols and the sulfoxide **4** in the presence of *p*-toluenesulfonic acid.

The adducts (**5**,**6**) given by the above Pummerer reaction can easily be desulfurized into the corresponding 2-arylbenzofurans (**7**,**8**) by heating Raney nickel in ethanol. Thus, the adducts **5a-e** and **6a-e** were converted into 2-(*p*-tolyl)benzofurans **7a-e** and 2-(*p*-chlorophenyl)benzofurans **8a-e**, respectively, in high yields.

Of the many methods for the preparation of 2-arylbenzofuran ring, the route[9] through the coupling reaction of an *o*-halophenol with a cuprous arylacetylide have been regarded as an efficient procedure. This method requires uncommon starting materials and lengthy reaction time.

In conclusion, we developed a new one-pot method for the construction of 2-arylbenzofurans (**2**,**5**,**6**) using substituted phenols and α-acylsulfoxides (**1**,**3**,**4**) in the presence of anhydrous *p*-toluenesulfonic acid. This method is generally applicable to benzofuran moiety having various aryl groups at the C-2 position.

The Pummerer reactions for utilizing α-acylsulfoxides has been proved to be useful to synthesize the naturally occurring products possessing 2-arylbenzofuran skeleton.

EXPERIMENTAL

General. All reagents and solvents were used without further purification. Melting points were determined with a Gallenkamp capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi R-1500 (FT, 60 MHz) spectrometer. Chemical shifts are expressed in δ units relative to tetramethylsilane as internal standard. IR spectra were recorded by using on a JASCO FT IR-300E spectrometer. Mass spectral data were obtained on a Hewlett Packard 5970 GC MS system. Silica gel 60 (70-230 mesh, E. Merck) was used for all column chromatographic separations.

ω-(Methylsufinyl)acetophenone (1). A solution of sodium metaperiodate (5.14 g, 24 mmol) in water (30 mL) was added in small portions to a stirred solution of 2-(methylthio)acetophenone (4 g, 24 mmol) in methanol (60 mL) at 0 °C and the mixture was further stirred at room temperature for 12 h. Inorganic materials were filtered off and the filtrate was extracted with chloroform (3 × 30 mL). The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residual solid was recrystallized from ethyl acetate to give **1** in 80% yield (3.49 g), mp. 86-87 °C (lit.[8] 86-86.5 °C); IR (KBr) 3044, 2933, 1675 (C=O), 1577, 1422, 1299, 1193, 1030 (S=O), 978 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 4.39 (d, J=3.5Hz, 2H), 7.48-7.62 (m, 3H), 7.98 (d, J=7.6Hz, 2H).

General procedure for the synthesis of 3-methylthio-2-phenylbenzofuran (2). A solution of **1** (1.1 mmol), substituted phenol (1.1 mmol), and anhydrous *p*-toluenesulfonic acid (3.3 mmol) in 1,2-dichloroethane (15 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 $MgSO_4$. The solvent was evaporated off, and the residue was purified by column chromatography (hexane/ethyl acetate=6/1) to give

2. **2a**: Yield 80%, mp 67-68 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.48 (s, 3H), 6.80-8.37 (m, 8H). **2b**: Yield 79%, mp 37-38 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J=7.6Hz, 3H), 2.38 (s, 3H), 2.80 (q, J=7.6Hz, 2H), 7.06-8.37 (m, 8H). **2c**: Yield 82%, colorless liquid, ^{1}H NMR ($CDCl_3$) δ1.33 (d, J=6.5Hz, 6H), 2.38 (s, 3H), 2.84-3.31 (m, 1H), 7.10-8.36 (m, 8H). **2d**: Yield 83%, colorless liquid, ^{1}H NMR ($CDCl_3$) δ1.42 (s, 9H), 2.39 (s, 3H), 7.24-8.38 (m, 8H). **2e**: Yield 78%, mp 115-116 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 2.47 (s, 3H), 2.53 (s, 3H), 6.98-8.33 (m, 7H). **2f**: Yield 53%, colorless liquid. ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.42 (s, 3H), 2.49 (s, 3H), 6.86-8.22 (m, 7H). The above spectral data for **2** are in accord with those reported.[6b]

ω-Methylsulfinyl-*p*-methylacetophenone (3). A suspension of NaH (60% mineral oil dispersion, 2 g, 50 mmol) in DMSO (30 mL) was heated with stirring at 70-75 °C for 40 min under Ar. After cooling to room temperature, THF (15 mL) was added to the reaction mixture. Ethyl *p*-toluate (3.28 g, 20 mmol) was added to the mixture at 0 °C, and the stirring was continued for 90 min at the room temperature. The reaction mixture was poured into water (150 mL), acidified with aqueous HCl to a pH 3-4, and throughly extracted with chloroform (3×30 mL). The combined organic layer was washed with water (3×30 mL), dried over $MgSO_4$, and evaporated off. The residual solid was recrystallized from ethyl acetate to give **3** in 74% yield (2.9 g), mp 113-114 °C; IR (KBr) 2998, 2911, 2362, 2344, 1671 (C=O), 1605, 1560, 1411, 1278, 1186, 1131, 1044 (S=O), 961 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 2.75 (s, 3H), 4.33 (d, J=4.1Hz, 2H), 7.31 (d, J=8.2Hz, 2H), 7.89 (d, J=8.2Hz, 2H); MS m/z 196 (M^+).

ω-Methylsulfinyl-*p*-chloroacetophenone (4). By the same procedure as described above for the preparation of **3**, compound **4** was obtained from ethyl *p*-chlorobenzoate (3.69 g, 20 mmol), NaH (60% mineral oil dispersion, 2 g, 50 mmol), and DMSO (30 mL) in 79% yield (3.42 g), mp 126-127 °C; IR (KBr) 3033, 2988, 2921, 2377, 2344, 1666 (C=O), 1588 1422, 1288, 1033 (S=O), 767 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 4.36 (d, J=3.9Hz, 2H), 7.49 (d, J=8.2Hz, 2H), 7.94 (d, J=8.2Hz, 2H); MS m/z 216 (M^+).

General procedure for the synthesis of 3-methylthio-2-(*p*-tolyl) benzofuran (5). By the same procedure as described above for the preparation of **2**, compound **5** was obtained from **3** (2 mmol), substituted phenol (2 mmol), and anhydrous *p*-toluenesulfonic acid (6 mmol). **5a**: Yield 78%, mp 97-98?; IR (KBr) 2918, 1499, 1472, 1332, 1272, 1256, 1202, 1187, 1078, 1016, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.40 (s, 3H), 2.48 (s, 3H), 7.11-7.57 (m, 5H), 8.17 (d, J=8.2Hz, 2H); MS m/z 268 (M^+). **5b**: Yield 83%, mp 66-67 °C; IR (KBr) 2959, 2918, 1498, 1468, 1412, 1275, 1255, 1202, 1185, 1081, 1021, 969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.31 (t, J=7.6Hz, 3H), 2.37 (s, 3H), 2.41 (s, 3H), 2.79 (q, J=7.6Hz, 2H), 7.11-7.54 (m, 5H), 8.17 (d, J=8.2Hz, 2H); MS m/z 282 (M^+). **5c**: Yield 82%, colorless liquid, IR (neat) 2952, 2920, 1613, 1501, 1470, 1420, 1255, 1204, 1184, 1078, 966 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.33 (d, J=7.0Hz, 6H), 2.38 (s, 6H), 2.82-3.38 (m, 1H), 7.02-7.54 (m, 5H), 8.17 (d, J=8.2Hz, 2H); MS m/z 296 (M^+). **5d**: Yield 86%, colorless liquid, IR (neat) 2916, 2920, 2867, 1501, 1471, 1363, 1332, 1278, 1259, 1205, 1185, 1077, 1019, 969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.37 (s, 6H), 7.11-7.69 (m, 5H), 8.17 (d, J=8.2Hz, 2H); MS m/z 310 (M^+). **5e**: Yield 67%, mp 125-126 °C; IR (KBr) 2917, 1497, 1456, 1442, 1254, 1120, 1187, 1076, 1065, 1012, 971 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ2.36(s, 3H), 2.42 (s, 3H), 7.15-7.68 (m, 5H), 8.17 (d, J=8.2Hz, 2H); MS m/z 288 (M^+).

General procedure for the synthesis of 3-methylthio-2-(*p*-chlorophenyl)benzofuran (6). By the same procedure as described above for the preparation of **2**, compound **6** was obtained from **4** (2 mmol), substituted phenol (2 mmol), and anhydrous *p*-toluenesulfonic acid (6 mmol). **6a**: Yield 87%, mp 107-108 °C; IR (KBr) 2920, 1486, 1470, 1401, 1254, 1202, 1090, 1074, 1010, 971 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ2.37 (s, 3H), 2.49 (s, 3H), 7.07-7.52 (m, 5H), 8.26 (d, J=8.7Hz, 2H); MS m/z 288 (M^+). **6b**: Yield 90%, mp 64-65 °C; IR (KBr) 2955, 2925, 2865, 1544, 1485, 1467, 1400, 1337, 1254, 1202, 1092, 1076, 1009, 966 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J=7.6Hz, 3H), 2.37 (s, 3H), 2.79 (q, J=7.6Hz, 2H), 7.11-7.52 (m, 5H), 8.25 (d, J=8.7Hz, 2H); MS m/z 302 (M^+). **6c**: Yield 84%, mp 81-82 °C; IR (KBr) 2952, 2919, 2862, 1545, 1486, 1463, 1422, 1402, 1383, 1254, 1204, 1177, 1094, 1077, 1012, 969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J=7.0Hz, 6H), 2.38 (s, 3H), 2.71-3.19 (m, 1H), 7.10-5.53 (m, 5H), 8.25 (d, J=8.7Hz, 2H); MS m/z 316 (M^+). **6d**: Yield 90%, mp 83-84 °C; IR (KBr) 2959,

1472, 1400, 1360, 1273, 1257, 1206, 1090, 1076, 1028, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.38 (s, 3H), 7.16-7.71 (m, 5H), 8.25 (d, J=8.2Hz, 2H); MS m/z 330 (M^+). **6e:** Yield 75%, mp 136-137 °C; IR (KBr) 2942, 2929, 1483, 1456, 1442, 1400, 1253, 1198, 1092, 1065, 1009, 971 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 7.18-7.69 (m, 5H), 8.25 (d, J=8.2Hz, 2H); MS m/z 308 (M^+).

General procedure for the synthesis of 2-(*p*-tolyl)benzofuran (7). Compound **5** (1.2 mmol) was heated at 60-65 °C in ethanol (30 mL) containing Raney nickel (W-2, 1.8 g) for 1h. The Raney nickel was removed by filtration and the solvent was evaporated off. The residual solid was recrystallized from ethanol to give **7**. **7a:** Yield 95%, mp 154-155 °C; IR (KBr) 2962, 1587, 1505, 1467, 1290, 1266, 1207, 1121, 1036, 1015, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.43 (s, 3H), 6.89 (s, 1H), 6.9 7-7.47 (m, 5H), 7.75 (d, J=8.2Hz, 2H); MS m/z 222 (M^+). **7b:** Yield 95%, mp 108-109 °C; IR (KBr) 2911, 1505, 1463, 1289, 1265, 1209, 1195, 1111, 1037, 1015, 932 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J=7.6Hz, 3H), 2.38 (s, 3H), 2.74 (q, J=7.6Hz, 2H), 6.89 (s, 1H), 7.01-7.51 (m, 5H), 7.74 (d, J=8.2Hz, 2H); MS m/z 236 (M^+). **7c:** Yield 95%, mp 97-98 °C; IR (KBr) 2956, 2866, 1506, 1471, 1381, 1354, 1288, 1264, 1208, 1160, 1112, 1034, 1015, 916 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J=7.0Hz, 6H), 2.38 (s, 3H), 2.68-3.23 (m, 1H), 6.90 (s, 1H), 7.03-7.50 (m, 5H), 7.74 (d, J=8.2Hz, 2H); MS m/z 250 (M^+). **7d:** Yield 95%, mp 124-125 °C; IR (KBr) 2956, 1505, 1473, 1458, 1364, 1328, 1277, 1208, 1166, 1127, 1036, 1016, 913 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.39 (s, 9H), 2.38 (s, 3H), 6.92 (s, 1H), 7.06-7.66 (m, 5H), 7.75 (d, J=8. 2Hz, 2H); MS m/z 264 (M^+). **7e:** Yield 95%, mp 177-178 °C; IR (KBr) 2955, 1585, 1504, 1444, 1262, 1206, 1163, 1114, 1060, 1035, 1015, 927 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ2.39 (s, 9H), 6.94 (s, 1H), 7.01-7.58 (m, 5H), 7.74 (d, J=8.2Hz, 2H); MS m/z 242 (M^+).

General procedure for the synthesis of 2-(*p*-chlorophenyl) benzofuran (8). By the same procedure as described above for the preparation of **7**, compound **8** was obtained from **6** (1 mmol), Raney nickel (1.5 g), and ethanol (25 mL). The residual solid was recrystallized from ethanol to give **8**. **8a:** Yield 88%, mp 186-187 °C; IR (KBr) 2913, 1579, 1488, 1462, 1404, 1261, 1210, 1195, 1092, 1034, 1009, 914 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 6.91 (s, 1H), 6.99-7.55 (m, 5H), 7.77 (d, J=8.8Hz, 2H); MS m/z 242 (M^+). **8b:** Yield 84%, mp 149-150 °C; IR (KBr) 2970, 1487, 1466, 1403, 1264, 1193, 1089, 1033, 1009, 911 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J=7.0Hz, 3H), 2.75 (q, J=7.6Hz, 2H), 6.94 (s, 1H), 7.01-7.50 (m, 5H), 7.78 (d, J=8.2Hz, 2H); MS m/z 256 (M^+). **8c:** Yield 89%, mp 152-153 °C; IR (KBr) 2958, 1580, 1488, 1469, 1403, 1355, 1267, 1160, 1117, 1103, 1091, 1031, 1009, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J=7.0Hz, 6H), 2.80-3.23 (m, 1H), 6.94 (s, 1H), 7.09-7.56 (m, 5H), 7.78 (d, J=8.8Hz, 2H); MS m/z 270 (M^+). **8d:** Yield 90%, mp 154-155 °C; IR (KBr) 2956, 1579, 1471, 1402, 1366, 1328, 1275, 1166, 1127, 1088, 1032, 1009, 913 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 6.96 (s, 1H), 7.10-7.57 (m, 5H), 7.78 (d, J=8.8Hz, 2H); MS m/z 284 (M^+). **8e:** Yield 76%, mp 151-152 °C; IR (KBr) 2957, 1599, 1581, 1486, 1443, 1324, 1273, 1260, 1163, 1091, 1061, 1033, 1011, 926 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.93 (s, 1H), 7.15-7.86 (m, 7H); MS m/z 262 (M^+).

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