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단 신

치환페놀류로부터 2,3-이치환벤조푸란 유도체의 합성

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Synthesis of 2,3-Disubstituted Benzofuran Derivatives from Substituted Phenols

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α-Chlorosulfides[1] in organic synthesis are well recognized as important sources of reactive electrophiles for alkylation reactions of aromatics, alkenes, alkynes, enolates and silyl enol ether derivatives of aldehydes and ketones, esters and lactones.

In the preceding papers[2] relating to the carbon-carbon bond formation using 1-acyl-1-thiocarbocations, we reported an excellent method for 2-(methyl and aryl)benzofurans by Friedel-Crafts reaction of substituted phenols with 1-acyl-1-chlorosulfides and successive desulfurization of the resulting 2-(methyl and aryl)-3-(methylthio)benzofurans. Also, we showed that the reaction of substituted phenols with α-(methylsulfinyl)acetone under Pummerer reaction conditions afforded a facile synthetic method for 2-methyl-3-(methylthio)benzofurans in one-pot.[3]

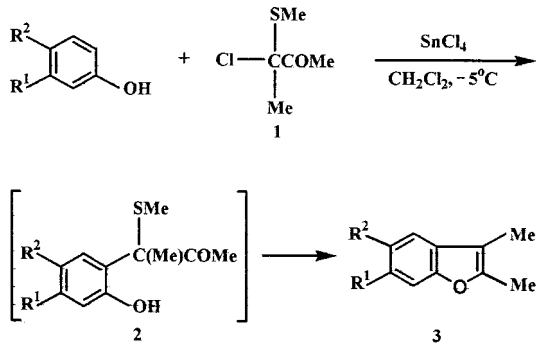
We now describe a novel reaction of substituted phenols with 1-acyl-1-thiocarbocations generated from the 3° chlorides (**1** and **4**) in the presence of Lewis acid, which provides an one-step route to 2,3-disubstituted benzofuran ring system (**3** and **5**).

3-Chloro-3-methylthio-2-butanone (**1**) was prepared from 3-methylthio-2-butanone by chlorination with N-chlorosuccinimide in carbon tetrachloride at low temperature according to the reported procedure.[4] The attempt for purification of **1** through vacuum distillation miscarried, and the crude material was promptly used in the next step. The structural assignments of **1** are based on ^{1}H NMR signals of the CH_3 groups. In the ^{1}H NMR spectra, the CH_3 groups appeared as three singlet signals in δ=1.99, 2.16, and 2.43 ppm.

Initially, a solution of *p*-cresol and the chloride **1** was treated with $SnCl_4$ in methylene chloride for 1h at -5 °C. The crude material was chromatographed to yield an unexpected product **3a** in the place of adduct **2**. The structural assignments of **3a** was made on the base of its spectral data (see "Experimental"), and particularly ^{13}C NMR spectral data are in accord with those reported.[5] The reaction of *p*-cresol with **1** in the presence of various Lewis acids shows that the order of activity of catalyst is $SnCl_4$ (53%) > $TiCl_4$ (44%) ≈ $AlCl_3$ (40%) ≫ $ZnCl_2$ (trace).

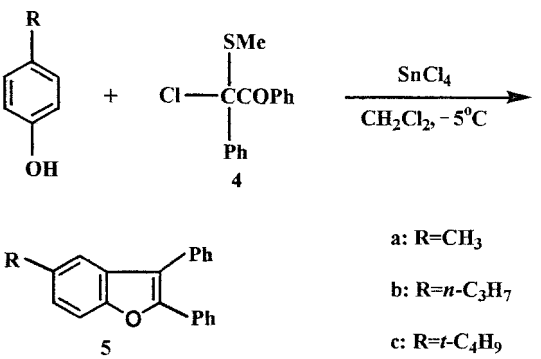
In order to check the generality of this reaction, we examined the reaction of **1** with other substituted phenols. The treatment of *p*-alkylphenols with **1** in the presence of $SnCl_4$ afforded the corresponding 2,3-dimethylbenzofuran derivatives **3b-e** in moderate yields. Similarly, 2,3-dimethyl-5,6-(methylenedioxy)benzofuran (**3f**) was obtained from the reaction of 3,4-(methylenedioxy)-phenol and the chloride **1** in 50% yield.

Hence, as shown in *Scheme* 1, the plausible mechanism for one-step synthesis of **3** can be explained by a successive dehydrocyclization and concurrent elimination of the methylthio group *via* Friedel-Crafts reaction interme-



a: R^1=H, R^2=CH_3, b: R^1=H, R^2=C_2H_5, c: R^1=H, R^2=*n*-C_3H_7
d: R^1=H, R^2=i-C_3H_7, e: R^1=H, R^2=*t*-C_4H_9, f: R^1-R^2=OCH_2O

Scheme 1.



a: R=CH_3
b: R=*n*-C_3H_7
c: R=*t*-C_4H_9

Scheme 2.

diate **2** being afforded under Lewis acid condition.

Next we accomplished the reaction of several *p*-alkyl phenols with 2-chloro-2-methylthio-2-phenylacetophenone (**4**) under the same reaction conditions described for the preparation of **3**. The 2,3-diphenylbenzofurans (**5**) were obtained from *p*-alkyl phenols and the chloride **4** in 35-40% yields.

Finally, we applied this reaction to naphthol isomers. Under the same reaction conditions described for the preparation of **3**, the reactions of 1-naphthol with the chlorides (**1** and **4**) in the presence of $SnCl_4$ afforded 2,3-disubstituted naphtho[1,2-b]furans (**6** and **7**) in 32% and 46% yields, respectively. The 2,3-disubstituted naphtho [2,1-b] furans (**8** and **9**) were also obtained by the treatment of 2-naphthol and the chlorides (**1** and **4**) with $SnCl_4$ in 48% and 46% yields, respectively.

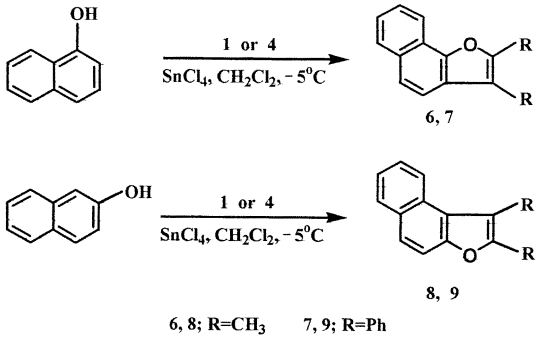
Several synthetic methods for 2,3-disubstituted benzofuran system have so far been reported in the literature. The following methods are representative: 1) amidoalkylation of aromatic compounds with methylglyoxalbismethylcarbamate in acid media,[6] 2) intramolecular [2+2] cycloaddition reactions of ketene and carbonyl groups,[7] and 3) the palladium catalyzed cyclization of propargylic *o*-(alkynyl)phenyl ethers.[8] The above methods require uncommon starting materials and definite anhydrous reaction conditions.

In summary, a new one-step synthesis for the construction of 2,3-disubstituted benzofuran ring (**3** and **5**) could be established by the treatment of substituted phenols with 1-acyl-1-thiocarbocationic intermediate generated from the 3° chlorides (**1** and **4**) in the presence of $SnCl_4$. The advantages of the present method are as follows; the diverse and available substituted phenols are directly utilized as the starting materials, and the reaction can be performed under mild conditions. As strategy directed toward biological potent substance possessing 2,3-disubstituted benzofuran moiety, the development of manifold 1-acyl-1-chlorosulfides is in progress.

EXPERIMENTAL

General. All reagents and solvents were used without further purification. Melting points were measured by a Gallenkamp capillary melting point apparatus and uncorrected. The ^1H NMR and ^{13}C NMR spectra were recorded using Jeol JNM ECP 400MHz spectrometer. Chemical shift values were reported in ppm downfield from tetramethylsilane as an internal standard. Mass data were obtained at 70 eV with a Hewlett Packard 5970 GC MS system by the electron impact (EI). Silica gel 60 (70-230 mesh, E. Merck) was used for all column chromatographic separations.

Preparation of 3-chloro-3-methylthio-2-butanone (1). 3-Methylthio-2-butanone (1.77 g, 15 mmol) was added to a stirred suspension of N-chlorosuccinimide (2.0 g, 15 mmol) in carbon tetrachloride (15 mL) at -10 °C under Ar, then the stirring was continued at the same temperature for 2h. The precipitated succinimide was filtered off and the filtrate was evaporated *in vacuo*. The crude material 1 was used for the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ1.99 (3H, s), 2.16 (3H, s), 2.43 (3H, s).



Scheme 3.

General procedure for the preparation of 2,3-dimethylbenzofurans (3). $SnCl_4$ (2.60 g, 10 mmol) was added to a stirred solution of **1** (2.29 g, 15 mmol) and a substituted phenol (10 mmol) in methylene chloride (20 mL) at -5 °C under Ar, then the stirring was continued at the same temperature for 1h. The reaction was quenched by the addition of water, then the mixture was extracted with methylene chloride (20 mL), and the extract was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/ethyl acetate=15:1) to give **3**.

2,3,5-Trimethylbenzofuran (3a). Yield 53%; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ2.05 (3H, s), 2.29 (3H, s), 2.39 (3H, s), 6.95 (1H, dd, J_1=8.20 Hz, J_2=1.48 Hz, 1H), 7.13 (1H, brs), 7.20 (1H, d, J=8.36 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ7.74, 11.63, 21.26, 109.34, 109.81, 118.41, 124.05, 130.50, 131.17, 150.43, 152.20; MS m/z 160 (M^+), 145, 128, 115, 91, 77, 63, 51.

2,3-Dimethyl-5-ethylbenzofuran (3b). Yield 47%; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.27 (3H, t, J=7.56 Hz), 2.12 (3H, s), 2.34 (3H, s), 2.72 (2H, q, J=7.56 Hz), 7.01 (1H, dd, J_1=8.36 Hz, J_2=1.64 Hz), 7.19 (brs, 1H), 7.25 (1H, d, J=8.36 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ7.87, 11.75, 16.41, 28.92, 109.50, 109.97, 117.23, 123.05, 130.50, 138.01, 150.53, 152.32; MS m/z 174 (M^+), 159, 144, 128, 115, 91, 77, 63, 51.

2,3-Dimethyl-5-(*n*-propyl)benzofuran (3c). Yield 54%. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ0.95 (3H, t, J=7.28 Hz), 1.62-1.72 (2H, m), 2.12 (3H, s), 2.34 (3H, s), 2.66 (2H, t, J=7.52 Hz), 6.99 (1H, dd, J_1=8.36 Hz, J_2=1.60 Hz), 7.18 (1H, brs), 7.25 (1H, d, J=8.20 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ7.89, 11.76, 13.83, 25.26, 38.10, 109.49, 109.86, 117.90, 123.61, 130.43, 136.37, 150.49, 152.35; MS m/z 188 (M^+), 173, 159, 144, 128, 115, 91, 77, 63, 51.

2,3-Dimethyl-5-(*i*-propyl)benzofuran (3d). Yield 48%. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ1.29 (6H, d, J=6.96 Hz), 2.13 (3H, s), 2.35 (3H, s), 2.95-3.05 (1H, m), 7.06 (1H, dd, J_1=8.44 Hz, J_2=1.72 Hz), 7.23 (1H, brs), 7.27 (1H, d, J=8.33 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ7.91, 11.78, 24.63, 34.19, 109.59, 109.97, 115.67, 121.70, 130.38, 142.76, 150.57, 152.34; MS m/z 188 (M^+), 173, 158, 145, 128, 115, 91, 79, 63, 51.

2,3-Dimethyl-5-(*t*-butyl)benzofuran (3e). Yield 53%. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ1.37 (9H, s), 2.14 (3H, s), 2.35 (3H, s), 7.25 (1H, d, J=1.88 Hz), 7.26 (1H, brs), 7.38 (1H, d, J=1.64 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ7.91, 11.77, 31.95, 34.67, 109.66, 109.74, 114.66, 120.76, 130.02, 145.01, 150.52, 152.01; MS m/z 202 (M^+), 187, 172, 159, 145, 131, 115, 91, 72, 63, 51.

2,3-Dimethyl-5,6-(methylenedioxy)benzofuran (3f). Yield 50%, pale yellow solid, mp 82-83; ^{1}H NMR (400 MHz, $CDCl_3$) δ2.07 (3H, s), 2.31 (3H, s), 5.94 (2H, s), 6.78 (1H, s), 6.88 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ7.95, 11.79, 93.06, 97.49, 100.95, 109.93, 123.69, 143.82, 144.97, 148.58, 149.84; MS m/z 190 (M^+), 175, 160, 145, 131, 116, 103, 94, 87, 77, 62, 51.

Preparation of 2-chloro-2-methylthio-2-phenylacetophenone (4). N-Chlorosuccinimide (4.0 g, 0.03 mol) was added to a stirred solution of 2-methylthio-2-phenylacetophenone (7.26 g, 0.03 mol) in carbon tetrachloride (40 mL) in small portions at 0 °C, then the stirring was continued at room temperature for 24 h. The precipitated succinimide was filtered off and the solvent was removed *in vacuo*. The crude product **4** was used for the next step without further purification. ^{1}H NM R (400 MHz, $CDCl_3$) δ2.10 (3H, s), 7.16-7.67 (10H, m); MS m/z 278 (M+2), 276 (M^+).

General procedure for the preparation of 2,3-diphenylbenzofurans (5). According to the same procedure for the preparation of **3**, compounds **5** were obtained from a substituted phenol (3 mmol), **4** (1.24 g, 4.5 mmol), and $SnCl_4$ (782 mg, 3.0 mmol).

2,3-Diphenyl-5-methylbenzofuran (5a). Yield 39%; White solid; mp 116-117 °C (from isopropyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ2.38 (3H, s), 7.10 (1H, brd, J=8.36 Hz), 7.22-7.28 (4H, m), 7.34-7.49 (6H, m), 7.61-

7.65 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ21.32, 110.58, 117.29, 119.72, 125.92, 126.89, 127.52, 128.17, 128.34, 128.91, 129.76, 130.30, 130.77, 132.34, 133.03, 150.58, 152.40; MS m/z 284 (M^+), 269, 255, 239, 226, 215, 202, 189, 178, 165, 134, 111, 101, 88, 77, 62, 51.

2,3-Diphenyl-5-(*n*-propyl)benzofuran (5b). Yield 35%: White solid; mp 79-80 °C (from isopropyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ0.93 (3H, t, J=7.16 Hz), 1.59-1.69 (1H, m), 2.64 (2H, t, J=7.44 Hz), 7.14 (1H, dd, J_1=7.04 Hz, J_2=1.44 Hz), 7.23-7.31 (4H, m), 7.38 (6H, m), 7.62-7.65 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ13.83, 25.23, 38.08, 110.61, 117.39, 119.21, 125.43, 126.95, 127.52, 128.18, 128.36, 128.94, 129.79, 130.22, 130.83, 133.08, 137.47, 150.64, 152.59; MS m/z 312 (M^+), 283, 268, 252, 239, 226, 201, 188, 176, 141, 128, 113, 88, 76, 63, 51.

2,3-Diphenyl-5-(*t*-butyl)benzofuran (5c). Yield 40%: White solid; mp 138-139 °C (from isopropyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ1.35 (9H, s), 7.23-7.29 (3H, m), 7.37-7.41 (2H, m), 7.44-7.52 (6H, m), 7.61-7.64 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$) δ31.85, 34.78, 110.43, 115.93, 117.71, 122.68, 126.96, 127.53, 128.16, 128.35, 128.98, 129.83, 130.85, 132.57, 133.08, 146.09, 150.76, 152.26; MS m/z 326 (M^+), 311, 296, 283, 270, 252, 239, 226, 215, 205, 189, 178, 165, 155, 141, 126, 115, 105, 91, 77, 63, 51.

2,3-Dimethylnaphtho[1,2-b]furan (6). According to the same procedure for the preparation of **3**, compound **6** was obtained from 1-naphthol (1.44 g, 10 mmol), **1** (2.29 g, 15 mmol) and $SnCl_4$ (2.6 g, 10 mm ol) in 32% yield (627 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 2.14 (3H, s), 2.41 (3H, s), 7.36-7.39 (1H, m), 7.45 (1H, d, J=8.60 Hz), 7.47-7.52 (1H, m), 7.56 (1H, d, J=8.64 Hz), 7.85 (1H, d, J=8.24 Hz), 8.23 (1H, d, J=8.24 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ7.97, 11.85, 110.78, 117.79, 119.69, 121.06, 122.44, 124.22, 125.59, 125.91, 128.29, 130.86, 148.84, 149.721; MS m/z 196 (M^+), 181, 165, 152, 139, 127, 115, 98, 82, 76, 63, 51.

2,3-Diphenylnaphtho[1,2-b]furan (7). According to the same procedure for the preparation of **3**, compound **7** was obtained from 1-naphthol (433 mg, 3 mmol), **4** (1.24 g, 4.5 mmol), and $SnCl_4$ (781 mg, 3.0 mmol) in 46% yield (442 mg) as white solid; mp 99-100 °C (from isopropyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.20-7.27 (4H, m), 7.34-7.39 (1H, m), 7.52-7.56 (8H, m), 7.68-7.74 (2H, m), 7.89 (1H, d, J=8.08 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ112.16, 119.52, 120.05, 123.04, 123.59, 124.22, 125.95, 126.17, 127.75, 128.17, 128.31, 128.38, 128.91, 129.35, 130.54, 130.84, 130.89, 134.68, 150.04, 151.38; MS m/z 320 (M^+), 301, 289, 275, 252, 249, 237, 214, 200, 188, 175, 159, 144, 131, 118, 105, 96, 87, 76, 62, 51.

2,3-Dimethylnaphtho[2,1-b]furan (8). According to the same procedure as described above for the preparation of **3**, compound **8** was obtained from 2-naphthol (1.44 g, 10 mmol), **1** (2.29 g, 15 mmol) and $SnCl_4$ (2.6 g, 10 mmol) in 48% yield (941 mg) as white solid; mp 33-34 °C (from isopropyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ2.45 (3H, s), 2.54 (3H, s), 7.41-7.45 (1H, m), 7.51-7.55 (1H, m), 7.56 (1H, s), 7.62 (1H, d, J=8.96 Hz), 7.92 (1H, d, J=8.56 Hz), 8.87 (1H, d, J=8.40 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ11.348, 11.703, 111.681, 112.049, 122.968, 123.183, 123.696, 123.906, 125.724, 128.678, 128.876, 130.612, 149.863, 151.209; MS m z 196 (M^+), 181, 165, 152, 139, 126, 115, 98, 82, 76, 63, 51.

2,3-Diphenylnaphtho[2,1-b]furan (9). According to the same procedure for the preparation of **3**, compound **9** was obtained from 2-naphthol (433 mg, 3 mmol), **4** (1.24 g, 4.5 mmol), and $SnCl_4$ (781 mg, 3.0 mmol) in 46% yield (442 mg) as white solid; mp 105-106 °C (from isopropyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.22-7.31 (3H, m), 7.35-7.39 (1H, m), 7.41-7.46 (3H, m), 7.50-7.61 (5H, m), 7.71 (2H, d, J=7.20 Hz), 7.86 (1H, d, J=8.08 Hz), 8.38 (1H, d, J=8.20 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ118.43, 118.76, 120.12, 121.19, 123.56, 125.16, 125.53, 126.32, 126.75, 127.60, 128.01, 128.36, 128.41, 128.95, 129.79, 130.88, 131.69, 132.92, 149.46, 149.95; MS m/z 320 (M^+), 302, 289, 276, 263, 250, 237, 215, 200, 189, 178, 160, 144, 131, 118, 107, 96, 87, 77, 63, 51.

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