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단 신

α-클로로-α-(메틸티오)페닐아세톤을 이용한 2-메틸-3-페닐벤조푸란 유도체의 합성

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Synthesis of 2-Methyl-3-phenylbenzofuran Derivatives Using α-Chloro-α-(methylthio)phenylacetone

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주제어: α-클로로-α-(메틸티오)페닐아세톤, 2-메틸-3-페닐벤조푸란 유도체, Friedel-Crafts 반응 조건

Keywords: α-chloro-α-(methylthio)phenylacetone, 2-methyl-3-phenylbenzofuran Derivatives, Friedel-Crafts Reaction Conditions

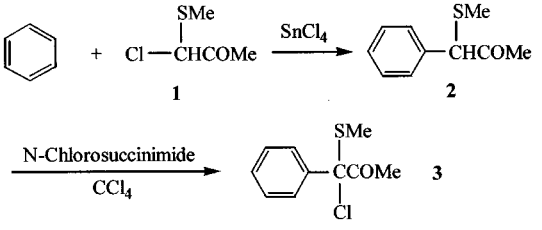
Benzofuran ring system occurs widely in natural products and in synthetic substances, which exhibit a variety of pharmacological properties.[1] A large number of synthetic routes towards the construction of benzofuran ring has so far been reported in the literature. Among the many methods on the formation of benzofuran ring starting from phenolic substrates, coupling reaction of *o*-halogenophenols with copper (I) arylacetylide to afford 2-substituted benzofurans appears as one of the most simple and general procedures.[2] However, the usefulness of this procedure is often limited by uncommon phenolic materials and a stoichiometric amount of the preformed organometallic reagent.

Recently we have developed an excellent method for 2-substituted benzofurans by one-pot reaction of substituted phenols with 1-acyl-1-thiocarbocations generated from 1-acyl-1-chlorosulfides under Friedel-Crafts reaction condition[3] or from β-ketosulfoxides under Pummerer reaction condition.[4]

In the preceding paper,[5] we showed that the reaction of substituted phenols with 3-chloro-3-methylthio-2-butanone in the presence of a Lewis acid provided a new method for synthesizing 2,3-disubstituted benzofurans. In this paper the method is applied to the synthesis of 2-methyl-3-phenylbenzofurans (**4**), in which α-chloro-α-(methylthio) phenylacetone (**3**) is employed as an electrophile in place of 3-chloro-3-methylthio-2-butanone.

The preparation of the starting material **3** was shown in *Scheme* 1. α-Chloro-α-(methylthio)acetone (**1**) was obtained from α-(methylthio) acetone by chlorination with N-chlorosuccinimide in carbon tetrachloride according to the reported method.[6] The Friedel-Crafts reaction of benzene with **1** in the presence of $SnCl_4$ gave α-(methylthio)phenylacetone (**2**) in 86% yield as described in the literature.[7] The treatment of **2** with N-chlorosuccinimide afforded the 3° chloride **3**, and this crude material was used for the praparation of **4** without further purification.

The previous study on the formation of 2,3-disubstituted benzofurans with 3-chloro-3-methylthio-

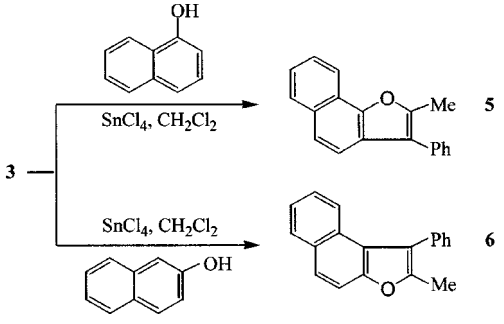


Scheme 1.

2-butanone under Friedel-Crafts reaction conditions[5] revealed that the order of Lewis acid activity is $SnCl_4$>$TiCl_4$≈$AlCl_3$>>$ZnCl_2$. On the basis of this information, $SnCl_4$ was used as a Lewis acid in the reaction of substituted phenols with **3**. Thus, treatment of *p*-cresol and **3** in methylene chloride with $SnCl_4$ at 0 °C gave 2,5-dimethyl-3-phenylbenzofuran (**4a**) in 51% yield. The structure of **4a** was confirmed by well-defined ^1H and ^{13}C NMR spectra, and mass spectra (see "Experimental").

We examined the reactions of other substituted phenols with **3**. The reactions took place smoothly in the presence of $SnCl_4$ giving the corresponding 2-methyl-3-phenylbenzofuran derivatives (**4b-e**) in moderate yields. Also 2-methyl-5,6-methylenedioxy-3-phenyl-benzofuran (**4f**) was obtained from the reaction of 3,4-(methylenedioxy)phenol and the chloride **3** in 48% yield. But in the reaction of 4-chlorophenol, α-(methylthio)phenylacetone (**2**) instead of a desired 2,3-disubstituted benzofuran could be obtained as a major product.

As the mechanism for the formation of 2,3-disubstituted benzofurans explained in our preceding work,[5] the mechanism for the formation of 2-methyl-3-phenylbenzofurans (**4**) is similarly considered by a successive dehydrocyclization and concurrent removal

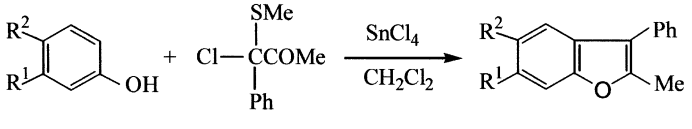


Scheme 3.

of methylthio group *via* Friedel-Crafts reaction intermediate afforded from substituted phenols and **3** under Lewis acid conditions.

In addition, we accomplished the reaction of naphthol isomers with α-chloro-α-(methylthio) phenylacetone (**3**) under the same reaction conditions as described for the preparation of **4**. The reactions of 1-naphthol and 2-naphthol with the chloride **3** in the presence of $SnCl_4$ gave 2-methyl-3-phenylnaphtho[1,2-b]furan (**5**) and 2-methyl-3-phenylnaphtho [2,1-b]furan (**6**) in 38% and 51% yields, respectively.

In conclusion, we developed a new one-pot method for synthesizing 2-methyl-3-phenylbenzofuran derivatives (**4**) using substituted phenols and α-chloro-α-(methylthio)phenylacetone (**3**) in the presence of $SnCl_4$. The present method could be applied to 2,3-disubstituted benzofuran moiety having various alkyl groups at the C-2 position and aryl groups at the C-3 position. As further work on the application of this method, the development of the manifold 3° chlorides such as α-chloro-α-(methylthio)arylacetone and the reactiv-



3 **4**

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 2.

ity of the 3° chlorides with substituted phenols are in progress.

EXPERIMENTAL

General. All chemicals were purchased from commercial sources and used without further purification. Melting point was measured using a Gallenkamp capillary melting point apparatus and uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a JNM-ECP 400 spectrometer (^{1}H NMR: 400 MHz and ^{13}C NMR: 100 MHz). Chemical shift values were reported in ppm downfield from tetramethylsilane as an internal standard. Mass spectra were obtained by electron impact (EI) method using a Hewlett Packard 5970 mass spectrometer. IR spectra were obtained on a JASCO FT/IR-300E spectrometer. Silica gel 60 (70-230 mesh, E. Merck) was used for all column chromatographic separations.

Preparation of α-chloro-α-(methylthio)acetone (1). N-Chlorosuccinimde (10.5 g, 80 mmol) was added to a stirred solution of α-(methylthio) acetone (8.2 g, 80 mmol) in carbon tetrachloride (60 mL) in small portions at 0 °C. This resulting mixture was stirred at room temperature for 3h. The precipitated succinimide was filtered off, and the filtrate was evaporated under reduced pressure. The residual oil was distilled to give **1** as a colorless oil. Yield 63% (6.8 g), bp: 55-56 °C/7 mm Hg (lit.[6] 76-77 °C/15 mmHg): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.37 (s, 3H), 5.38 (s, 1H).

Preparation of α-(methylthio)phenylacetone (2). This compound was prepared according to the procedure reported in the literature.[4] $SnCl_4$ (13.0 g, 50 mmol) was added to a stirred solution of **1** (6.9 g, 50 mmol) in benzene (80 mL) at 0 °C under Ar. The reaction mixture was stirred at the same temperature for 1h. The reaction was quenched by the addition of water and extracted with benzene, and dried over anhydrous $MgSO_4$.

The solvent was evaporated off, and the residue purified by column chromatography (benzene) to give **2** as a colorless oil. Yield 86%(7.7 g); ^{1}H NMR (400 MHz, $CDCl_3$): 2.01(s, 3H), 2.17(s, 3H), 4.53 (s, 1H), 7.37(s, 5H); IR(neat): 3407, 3060, 3027, 2983, 2918, 2813, 1712(CO), 1597, 1493, 1423, 1354, 1258, 1150 cm^{-1}.

Preparation of α-chloro-α-(methylthio)phenylacetone (3). N-Chlorosuccinimide (1.34 g, 10 mmol) was added to a stirred solution of the compound **2** (1.8 g, 10 mmol) in carbon tetrachloride (20 mL) in small portions at 0 °C, then the stirring was continued at room temperature for 20 h. The precipitated succinimide was filtered and the filtrate was removed under reduced pressure. The crude material **3** was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H), 2.19 (s, 3H), 7.27-7.66 (m, 5H); MS m/z: 216 (M+2), 214 (M$^+$).

General procedure for the preparation of 2-methyl-3-phenylbenzofurans (4). $SnCl_4$ (1.56 g, 6 mmol) was added to a stirred solution of **3** (10 mmol) and a substituted phenol (6 mmol) in methylene chloride (20 mL) at 0 °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=20/1) to give **4**.

2,5-Dimethyl-3-phenylbenzofuran (4a). Yield 51%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.47 (s, 3H), 7.03 (dd, J_1=8.40 Hz, J_2=1.32Hz, 1H), 7.28-7.35 (m, 3H), 7.40-7.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.76, 21.34, 110.20, 116.64, 119.17, 124.65, 126.82, 128.70, 128.78, 128.90, 131.96, 132.97, 151.34, 152.41; MS m/z: 222 (M$^+$), 207, 189, 178, 165, 145, 115, 102, 89, 77, 63, 51; IR (neat): 3055, 2918, 2857, 2734, 1613, 1454, 1256, 1193 cm^{-1}.

5-Ethyl-2-methyl-3-phenylbenzofuran (4b). Yield 48%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, J=7.64 Hz, 3H), 2.50 (s, 3H), 2.71 (q, J=7.64 Hz, 2H), 7.08 (d, J=8.36 Hz, 1H), 7.31-7.38 (m, 3H), 7.44-7.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.80, 16.44, 28.96, 110.35, 116.76, 118.01, 123.63, 126.84, 128.69, 128.77, 128.94,

133.03, 138.74, 151.40, 152.53; MS m/z: 236 (M^+), 221, 202, 189, 178, 165, 139, 115, 103, 91, 77, 63, 51; IR (neat): 3024, 2962, 2925, 2869, 1621, 1471, 1388, 1254, 1193 cm^{-1}.

2-Methyl-3-phenyl-5-propylbenzofuran (4c). Yield 50%, colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J*=7.32 Hz, 3H), 1.59-1.68 (m, 2H), 2.49 (s, 3H), 2.64 (t, *J*=7.34 Hz, 2H), 7.06 (dd, J_1=8.40 Hz, J_2=1.60 Hz, 1H), 7.31-7.38 (m, 3H), 7.42-7.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.81, 13.80, 25.27, 38.11, 110.23, 116.73, 118.64, 124.17, 126.83, 128.55, 128.69, 128.93, 133.04, 137.08, 151.35, 152.56; MS m/z: 250 (M^+), 221, 202, 189, 178, 165, 152, 115, 103, 91, 77, 65, 51; IR (neat) 3055, 2953, 2851, 1620, 1476, 1365, 1254, 1190 cm^{-1}.

2-Methyl-3-phenyl-5-isopropylbenzofuran (4d). Yield 51%, colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, *J*=6.96 Hz, 6H), 2.48 (s, 3H), 2.35 (s, 3H), 2.93-3.02 (m, 1H), 7.11 (dd, J_1=8.00 Hz, J_2=1.60 Hz, 1H), 7.29-7.37 (m, 2H), 7.39-7.51 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$):12.77, 24.58, 34.26, 110.38, 116.50, 116.86, 122.19, 126.63, 128.54, 128.71, 128.95, 133.07, 143.45, 151.41, 152.59; MS m/z: 250 (M^+), 235, 220, 207, 191, 178, 165, 117, 103, 77, 63, 51; IR (neat): 3056, 2958, 2868, 1619, 1472, 1362, 1254, 1197 cm^{-1}.

5-*tert*-Butyl-2-methyl-3-phenylbenzofuran (4e). Yield 56%, colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9H), 2.47 (s, 3H), 7.28-7.36 (m, 3H), 7.42-7.53 (m, 4H), 7.57 (d, *J*=1.64 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):12.77, 31.90, 34.72, 110.05, 115.39, 117.02, 121.36, 126.83, 128.34, 128.75, 128.97, 133.09, 145.69, 151.42, 152.26; MS m/z: 264 (M^+), 249, 234, 221, 207, 189, 178, 165, 152, 110, 103, 91, 77, 63, 51; IR (neat) 3058, 2967, 2868, 1620, 1476, 1264, 1206, 1103 cm^{-1}.

2-Methyl-5,6-methylenedioxy-3-phenylbenzofuran (4f). Yield: 48%, a white solid; mp: 112-113 (isopropyl ether); ^1H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 5.95 (s, 2H), 6.94 (s, 1H), 6.95 (s, 1H), 7.32-7.37 (m, 1H), 7.43-7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.81, 93.19, 98.22, 101.12, 117.24, 121.92, 126.89, 128.74, 132.86, 144.36, 145.39, 148.89, 150.53; MS m/z: 252 (M^+), 237, 215, 189, 165, 147, 105, 77, 62, 51; IR (KBr): 3052, 2909, 1632, 1460, 1335, 1291, 1178, 1123, 1032 cm^{-1}.

2-Methyl-3-phenylnaphtho[1,2-b]furan (5). According to the same procedure for the preparation of **4**, compound **5** was obtained from 1-naphthol (865 mg, 6 mmol), **3** (2.15 g, 10 mmol) and $SnCl_4$ (1.56 g, 6 mmol) in 38% yield (588 mg) as a viscous semisolid. ^1H NMR (400 MHz, $CDCl_3$): δ 2.61 (s, 3H), 7.33-7.38 (m, 1H), 7.41-7.58 (m, 6H), 7.62 (d, *J*=8.52 Hz, 1H), 7.65 (d, *J*=8.52 Hz, 1H), 7.89 (d, *J*=8.24 Hz, 1H), 8.29 (d, *J*=8.24 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.93, 118.13, 118.31, 119.78, 121.15, 123.12, 123.95, 124.66, 126.16, 126.93, 128.28, 128.75, 128.98, 131.08, 132.96, 149.21, 150.49; MS m/z: 258 (M^+), 239, 228, 215, 202, 181, 152, 129, 114, 101 88, 77, 63, 51; IR (neat): 3052, 3034, 1614, 1581, 1496, 1443, 1379, 1175 cm^{-1}.

2-Methyl-3-phenylnaphtho[2,1-b]furan (6). According to the same procedure for the preparation of **4**, compound **6** was obtained from 2-naphthol (865 mg, 6 mmol), **3** (2.15 g, 10 mmol), and $SnCl_4$ (1.56 g, 6 mmol) in 51% yield (790 mg) as a viscous semisolid. ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 7.23-7.28 (m, 1H), 7.32-7.37 (m, 1H), 7.40-7.49 (m, 5H), 7.61 (d, *J*=8.96 Hz, 1H), 7.64 (d, *J*=8.96 Hz, 1H), 7.77 (d, *J*=8.32 Hz, 1H), 7.87 (d, *J*=8.20 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.27, 112.02, 118.95, 122.28, 123.17, 123.94, 124.49, 125.57, 127.52, 127.89, 128.58, 128.78, 130.48, 130.74, 134.18, 151,21, 151.23; MS m/z: 258 (M^+), 239, 229, 215, 202, 181, 152, 113, 101, 88, 77, 63, 51; IR (neat): 3053, 2917, 2851, 1622, 1596, 1578, 1496, 1442, 1395, 1376, 1271, 1216 cm^{-1}.

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