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단 신

2-Chloro-2-(methylthio)acetophenone을 이용한 2-페닐벤조[b]퓨란 유도체의 합성

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Synthesis of 2-Phenylbenzo[b]furan Derivatives Using 2-Chloro-2-(methylthio)acetophenone

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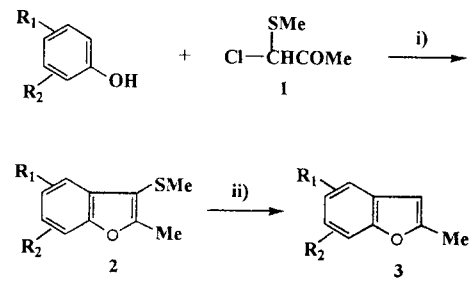
It is well known that 2-arylbenzo[b]furan derivatives are occured in natural products such as *Styrax obassia*,[1] *Sophora tomentosa*,[2] and *Krameria ramosissima*.[3]

In the course of our search on the carbon-carbon bond formation utilizing 1-acyl-1-thiocarbocationic intermediates, we showed that the reaction of substituted phenols with α-chloro-α-(methylthio)acetone (**1**) in the presence of Lewis acid provided a convenient method for the 2-methylbenzo[b]furans (**3**) through the reductive desulfurization of the resulting products (**2**) (*Scheme* 1).[4] The present paper describes the one-step synthesis for 2-phenylbenzo[b]furan derivatives from the reaction of phenol or cresol isomers with 2-chloro-2-(methylthio) acetophenone in the presence of zinc chloride.

Many procedures have been reported for the preparation of 2-phenylbenzofuran ring.[5-9] Among them, the most frequently employed method[5] is based upon the cyclodehydration reaction of aryloxyacetone moiety with standard dehydrating reagents (H_2SO_4, $ZnCl_2$, $POCl_3$, KOH or PPA).

As shown in *Scheme* 2, the treatment of *p*-cresol and 2-chloro-2-(methylthio)acetophenone (**4**) with zinc chloride in methylene chloride at 0 °C gave 5-methyl-3-methylthio-2-phenylbenzo[b]furan (**5**) in 89% yield. Hence, the mechanism for the one-step synthesis of **5** is explained by a successive dehydrocyclization of the Friedel-Crafts reaction intermediate being afforded under Lewis acid condition. The compound (**5**) was desulfurized by heating with Raney nickel in ethanol to give 5-methyl-2-phenylbenzo[b]furan (**6**) in 86% yield.

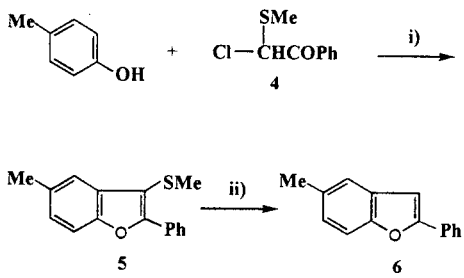
We also examined the reaction of phenol, *o*- and *m*-cresols with **4** (*Scheme* 3). The treatment of phenol and **4** with zinc chloride gave 3-methylthio-2-phenylbenzo-[b]furan (**7**) in 31% yield and 1,1-di(methylthio)-acetophenone (**8**)[10] as a by-product. Similarly, 7-methyl-3-methylthio-2-phenylbenzo[b]furan (**9**) and 6-methyl-3-methylthio-2-phenylbenzo[b]furan (**10**) were obtained from *o*- and *m*-cresols in 23% and 46% yields, res-



R_1=R_2=H; R_1=H, R_2=alkyl; R_1=R_2=alkyl

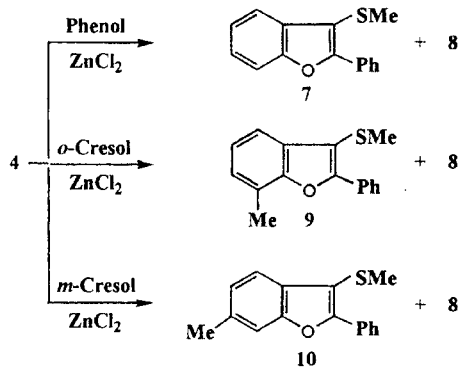
i) Lewis acid ii) Raney-nickel

Scheme 1.



i) $ZnCl_2$, 0°C, 1h
ii) Raney-nickel (W-2), EtOH, 60-70°C, 1h

Scheme 2.



8; 1,1-di(methylthio)acetophenone

Scheme 3.

pectively. In these cases thioacetal (**8**) was also formed as a by-product.

In conclusion, a new route for the formation of 2-phenylbenzo[b]furan ring could be established by the treatment of substituted phenols with 1-acyl-1-thiocarbocationic intermediate generated from the compound (**4**) in the presence of zinc chloride. The advantages of the present method are as follows: the diverse and easily available substituted phenols are directly utilized as the starting materials, and the sequence of reactions can be carried out under mild conditions in good yields.

The reactions of a series of substituted phenols with **4** and its application for the synthesis of natural products containing the skeletal structure of 2-arylbenzo[b]furan ring are in progress, and the results of these investigations will be reported in the near future.

EXPERIMENTAL

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

2-Chloro-2-(methylthio)acetophenone (4). *N*-Chlorosuccinimide (5.6 g, 0.042 mol) was added to a stirred solution of 2-(methylthio)acetophenone (7 g, 0.042 mol) in carbon tetrachloride (35 mL) in small portions at 0 °C and the stirring was continued at room temperature for 6h. The precipitated succinimide was filtered off and the solvent was removed *in vacuo*. The residual oil was distilled at 95 °C/7 mmHg to give **4** (5.2 g, 62%). IR (neat) 3061, 2987, 2923, 1690, 1595, 1578, 1448, 1320, 1271, 1206 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ2.25 (s, SCH_3, 3H), 6.32 (s, CH, 1H), 7.26~8.08 (m, ArH, 5H); MS (m/z) 200[M$^+$], 166, 120, 105, 91, 77, 61, 51.

5-Methyl-3-methylthio-2-phenylbenzo[b]furan (5). To a stirred solution of *p*-cresol (162 mg, 1.5 mmol) and **4** (300 mg, 1.5 mmol) in methylene chloride (5 mL) at 0 °C was added zinc chloride (218 mg, 1.6 mmol) under N_2 atmosphere, and the stirring was continued at the same temperature for 1h. The reaction was quenched by the addition of water and the mixture was extracted with methylene chloride (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate=15/1) to give **5** (340 mg, 89%) as a white solid. mp 67~68 °C; IR (KBr) 2917, 1472, 1443, 1255, 1203, 1084, 1066 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ2.37 (s, SCH_3, 3H), 2.48 (s, CH_3, 3H), 6.82~8.37 (m, ArH, 8H); MS (m/z) 254[M$^+$], 211, 179, 152, 127, 89, 77, 51.

5-Methyl-2-phenylbenzo[b]furan (6). Compound **5** (300 mg, 1.18 mmol) was heated at 60~70 °C in ethanol (15 mL) containing Raney nickel (W-2, 3 g) for 1h. The Raney nickel was removed by filtration and the solvent was evaporated off. The residue was purified by column chromatography (hexane/ethyl acetate=15/1) to give **6** (210 mg, 86%) as a white solid. mp 129~130 °C; IR (KBr) 3013, 2914, 1466, 1444, 1266, 1199, 1039 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 2.44 (s, CH_3, 3H), 6.72~8.21 (m,

ArH, 8H); MS (m/z) 208[M$^+$], 165, 152, 139, 104, 76, 51, 39.

3-Methylthio-2-phenylben[b]zofuran (7). By the same procedure as described above for the preparation of **5**, compound (**7**) was obtained from phenol (234 mg, 2.49 mmol) in 31% yield (185 mg) as an oil. IR (neat) 3060, 2920, 1489, 1454, 1441, 1254, 1201, 1085, 1066, 1032 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ2.39 (s, SCH_3, 3H), 7.26 ~8.39 (m, ArH, 8H); MS (m/z) 240[M$^+$], 197, 165, 152, 121, 89, 77, 39.

7-Methyl-3-methylthio-2-phenylbenzo[b]furan (9). By the same procedure as described above for the preparation of **5**, compound (**9**) was obtained from o-cresol (269 mg, 2.49 mmol) in 23% yield (145 mg) as an oil. IR (neat) 3059, 2922, 1479, 1442, 1417, 1205, 1086, 1065, 1030 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ2.38 (s, SCH_3, 3H), 2.58 (s, CH_3, 3H), 7.12~8.39 (m, ArH, 8H); MS (m/z) 254[M$^+$], 211, 178, 152, 127, 105, 77, 51.

6-Methyl-3-methylthio-2-phenylbenzo[b]furan (10). By the same procedure as described above for the preparation of **5**, compound (**10**) was obtained from *m*-cresol (269 mg, 2.49 mmol) in 46% yield (290 mg) as a white solid. mp 75~76 °C; IR (KBr) 3049, 2916, 1489, 1437, 1417, 1331, 1128, 1084, 1065 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ2.38 (s, SCH_3, 3H), 2.50 (s, CH_3, 3H), 7.06~8.35 (m, ArH, 8H); MS (m/z) 254[M$^+$], 211, 178, 165, 127, 104, 77, 51.

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10. 8 mp 69-70°C; IR (KBr) 3060, 2981, 2916, 1674, 1595, 1579, 1446, 1319, 279, 1192, 1003 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 2.15 (s, SCH_3×2, 6H), 5.31 (s, CH, 1H), 7.2~8.07 (m, ArH, 5H).