Synthesis of 2-Arylbenzo[b]furan Derivatives from Substituted Phenols

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As a part of the constituents isolated from *Krameria ramostisima*, *Machilus glaucescens*, *Myroxylon balansae*, *Sophora tomentosa*, *Styax obaia*: and *Zanthoxylum ailanthoides*, there are many well-known natural products possessing a benzo[b]furan skeleton which has the various aryl groups in the 2-position.

Recently, we showed an excellent method for preparation of 2-methylbenzo[b]furans from the one step reaction of substituted phenols with 1-chloro-1-(methylthio)acetone (1) in the presence of Lewis acid (Scheme 1). For our basic research programs toward the synthesis of natural products containing 2-arylbenzo[b]furan ring, we employed 2-chloro-2-(methylthio)acetophenone (2) instead of 1. Thus it was confirmed that 2-phenylbenzo[b]furans ring could be prepared by the reaction of phenol and cresol isomer with 2 in the presence of zinc chloride.*

As shown in Scheme 2, the present paper describes a general synthetic method for 2-arylbenzo[b]furan derivatives (6, 7) by the reaction of substituted phenols with 2 as well as 2-chloro-2-methylthio-(3,4'-methylenedioxy)acetophenone (3) and successive desulfurization of the resulting 2-aryl-3-methylthiobenzo[b]furans (4, 5). The treatment of substituted phenols and 2 with zinc chloride in methylene chloride at 0°C gave the corresponding 3-methylthio-2-phenylbenzo[b]furans (4) in high yields. The compounds 4 were easily desulfurized by heating with Raney nickel in ethanol to give 2-phenylbenzo[b]furans (6) in good yields.

Next we examined the reaction of substituted phenols with 3 under the same conditions as the preparation of 4. The 2-(3',4'-methylenedioxyphenyl)-3-(methylthio)benzo[b]furans (5) were obtained from substituted phenols and
3. The desulfurization of 5 with Raney nickel in boiling ethanol afforded the corresponding 2-(3',4'-methylenedioxyphenyl)benzo[b]furan (7).

Of the several methods available for the preparation of 2-arylbenzo[b]furan ring, the route through the reaction of an o-halogenophenol with a copper(I) arylacetylide seems to be an useful procedure for 2-arylbenzo[b]furan construction. However, this route requires longer reaction time and the yield is very low.

In summary, our route for the formation of 2-arylbenzo[b]furan derivatives (6,7) consists of two steps: i) a successive dehydrocyclization of Friedel-Crafts reaction intermediate which was prepared from the treatment of substituted phenols with the chlorides 2,3 in the presence of zinc chloride; ii) the reductive desulfurization of the resulting products 4,5. Now the application for total synthesis of natural products involving the skeletal structure of various benzo[b]furan rings with 3,4-methylenedioxyphenyl and highly methoxylated phenyl groups in the 2-position is in progress.

**EXPERIMENTAL**

Melting point was determined on a Gallenkamp melting point apparatus and uncorrected. 1H NMR spectra were recorded on a Hitachi R-1500 (FT, 60MHz) spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. Mass spectra were measured with a Hewlett Packard 5970 GC/MS system. Silica gel 60 (70-230 mesh, E. Merck) was used for column chromatography.

**Synthesis of 3-Methylthio-2-phenylbenzo[b]furans 4: General Procedure.** ZnCl₂ (218 mg, 1.6 mmol) was added to a stirred solution of 2 (310 mg, 1.5 mmol) and a substituted phenol (1.5 mmol) in CH₂Cl₂ (5 mL) at 0°C under N₂ atmosphere, and stirring was continued at the same temperature for 1h. The reaction was quenched by the addition of water, then the mixture was extracted with CH₂Cl₂ (10 mL), and the extract was dried over anhydrous MgSO₄. The solvent was removed in vacuo and the residue was purified by column chromatography (hexane/ethyl acetate=15/1) to give 4. 4a: Yield 89%; mp. 67-68°C; 1H NMR (CDCl₃) δ 8.37 (s, 3H), 2.48 (s, 3H), 6.82-8.37 (m, 8H); IR (KBr) 2917, 1472, 1443, 1255, 1203, 1084, 1066 cm⁻¹; MS: m/z 254 (M⁺).

**Synthesis of 2-(3',4'-Methylenedioxyphenyl)-3-methylthio benzo[b]furans 5: General Procedure.** By the same procedure as described above for the preparation of 4, compounds (5) were obtained from 3 (228 mg, 0.93 mmol), a substituted phenol (0.93 mmol) and ZnCl₂ (150 mg, 1.1 mmol). The residue was purified by column chromatography (benzene). 5a: Yield 76%; mp. 120-121°C; 1H NMR (CDCl₃) δ 8.36 (s, 3H), 2.47 (s, 3H), 6.02 (s, 2H), 6.83-7.89 (m, 6H); IR (KBr) 3020, 2959, 2863, 1649, 1339, 1256, 1066 cm⁻¹; MS: m/z 268 (M⁺). 4b: liquid; Yield 92%; 1H NMR (CDCl₃) δ 1.33 (dt, 6H, J=6.5Hz), 2.38 (s, 3H), 2.84-3.01 (m, 1H), 7.10-8.36 (m, 8H); IR (neat) 2958, 1734, 1684, 1558, 1457, 1066 cm⁻¹; MS: m/z 282 (M⁺). 5a: liquid; Yield 91%; 1H NMR (CDCl₃) δ 1.43 (s, 9H), 2.39 (s, 3H), 7.26-8.38 (m, 8H); IR (neat) 3063, 2961, 2867, 1558, 1520, 1489 cm⁻¹; MS: m/z 296 (M⁺).

Yield 80%; mp. 116-117°C; 1H NMR (CDCl₃) δ 8.38 (s, 3H), 2.46 (s, 3H), 2.53 (s, 3H), 6.97-8.33 (m, 7H); IR (KBr) 2918, 1473, 1420, 1204, 1067, 1031 cm⁻¹; MS: m/z 268 (M⁺). 4e: liquid; Yield 51%; 1H NMR (CDCl₃) δ 1.28 (s, 3H), 2.42 (s, 3H), 2.49 (s, 3H), 6.85-8.21 (m, 7H); IR (neat) 2917, 2857, 1621, 1486, 1330, 1092 cm⁻¹; MS: m/z 268 (M⁺).

Yield 76%; mp. 120-121°C; 1H NMR (CDCl₃) δ 8.36 (s, 3H), 2.47 (s, 3H), 6.02 (s, 2H), 6.83-7.89 (m, 6H); IR (KBr) 3020, 2959, 2863, 1649, 1339, 1256, 1066 cm⁻¹; MS: m/z 268 (M⁺). 4f: liquid; Yield 51%; 1H NMR (CDCl₃) δ 1.28 (s, 3H), 2.42 (s, 3H), 2.49 (s, 3H), 6.85-8.21 (m, 7H); IR (neat) 2917, 2857, 1621, 1486, 1330, 1092 cm⁻¹; MS: m/z 268 (M⁺).
(s, 3H), 6.95-7.82 (m, 7H); IR (KBr) 2957, 1468, 1128, 1038 cm\(^{-1}\); MS: m/z 236 (M\(^+\)).

**Synthesis of 2-Phenylbenzo[b]furans 6: General Procedure.** Raney nickel (W-2, 2.4 g) was added to a solution of 4 (200-400 mg) in EtOH (20 mL). The mixture was heated at 60-70°C for 1 h. The Raney nickel was filtered off and the solvent was evaporated off. The residue was purified by column chromatography (hexane/ethyl acetate=15/1) to give 6a: Yield 86%; mp 129-130°C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.44 (s, 3H), 6.72-8.21 (m, 9H); IR (KBr) 3013, 2914, 1466, 1366, 1199, 1093 cm\(^{-1}\); MS: m/z 208 (M\(^+\)); 6b: Yield 81%; mp 76-77°C; \(^1\)H NMR(CDCl\(_3\)) \(\delta\) 1.28 (t, 3H, J=7.6Hz), 2.75 (q, 2H, J=7.6Hz), 6.95-7.87 (m, 9H); IR (KBr) 2959, 1560, 1465, 1267, 1038 cm\(^{-1}\); MS: m/z 224 (M\(^+\)); 6c: Yield 81%; mp 87-88°C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.13 (s, 9H), 6.97-7.94 (m, 9H); IR (KBr) 2957, 1468, 1259, 1160, 1020 cm\(^{-1}\); MS: m/z 236 (M\(^+\)).

**Synthesis of 2-(3,4-Methylenedioxyphenyl)benzo[b]furans 7: General Procedure.** By the same procedure as described above for the preparation of 6, compounds (7) were obtained from 5 (150-250 mg) and Raney nickel (1.5-3.0 g). The residue was purified by column chromatography (benzene). 7a: Yield 71%; mp 132-133°C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.43 (s, 3H), 6.01 (s, 2H), 6.79-7.45 (m, 7H); IR (KBr) 2987, 1462, 1230, 1200, 1107, 1037 cm\(^{-1}\); MS: m/z 252 (M\(^+\)).

**REFERENCES**


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