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단 신

치환페놀류로부터 2-아릴벤조[b]푸란 유도체의 합성

崔洪大*・徐弼子・孫炳華†
동의대학교 화학과・기초과학연구소
†부경대학교 자연과학대학 화학과
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Synthesis of 2-Arylbenzo[b]furan Derivatives from Substituted Phenols

Hong-Dae Choi*, Pil-Ja Seo and Byeng-Wha Son†
Department of Chemistry and Research Institute of Basic Science, Dongeui University, Pusan 614-714, Korea
†Department of Chemistry, Pukyong National University, Pusan 608-737, Korea
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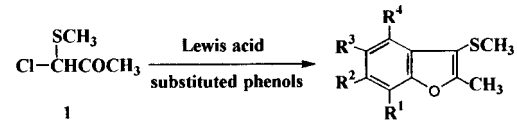
As a part of the constituents isolated from *Krameria ramosissima*,[1] *Machilus glaucescens*,[2] *Myroxylon balsamum*,[3] *Sophora tomentosa*,[4] *Styrax obassia*,[5] and *Zanthoxylum ailanthoides*,[6] there are many well known natural products possessing a benzo[b]furan skeleton which has the various aryl groups in the 2-position.

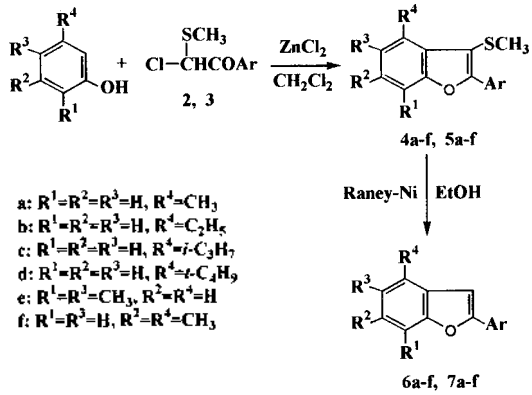
Recently, we showed an excellent method for preparation of 2-methylbenzo[b]furans from the one step reaction of substituted phenols with 1-chloro-1-(methylthio) acetone (**1**) in the presence of Lewis acid[7] (*Scheme* 1). For our basic research programs toward the synthesis of natural products containing 2-arylbenzo[b]furan ring, we employed 2-chloro-2-(methylthio)acetophenone (**2**) instead of **1**. Thus it was easily 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[8].

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



Scheme 1.



Scheme 2.

3. The desulfurization of **5** with Raney nickel in boiling ethanol afforded the corresponding 2-(3',4'-methylenedioxyphenyl)benzo[b]furans (**7**).

Of the several methods available for the preparation of 2-arylbenzo[b]furan ring, the route[9] 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 Freidel-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. ^{1}H 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. $ZnCl_2$ (218 mg, 1.6 mmol) was added to a stirred solution of **2** (300 mg, 1.5 mmol) and a substituted phenol (1.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C under N_2 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 CH_2Cl_2 (10 mL), and the extract was dried over anhydrous $MgSO_4$. 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 ^{1}H NMR ($CDCl_3$) δ2.37 (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^+). **4b**: Yield 90%; mp. 37-38 °C; ^{1}H NMR ($CDCl_3$) δ1.31 (t, 3H, J=7.6Hz), 2.38 (s, 3H), 2.80 (q, 2H, J=7.6Hz), 7.08-8.37 (m, 8H); IR (KBr) 3020, 2959, 2863, 1469, 1339, 1256, 1066 cm^{-1}; MS: m/z 268 (M^+). **4c**: liquid; Yield 92%; ^{1}H NMR ($CDCl_3$) δ1.33 (d, 6H, J=6.5Hz), 2.38 (s, 3H), 2.84-3.31 (m, 1H), 7.10-8.36 (m, 8H); IR (neat) 2958, 1734, 1684, 1558, 1457, 1066 cm^{-1}; MS: m/z 282 (M^+). **4d**: liquid; Yield 91%; ^{1}H NMR ($CDCl_3$) δ1.43 (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^+). **4e**: Yield 80%; mp. 116-117 °C; ^{1}H NMR ($CDCl_3$) δ2.38 (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^+). **4f**: liquid; Yield 51%; ^{1}H NMR ($CDCl_3$) δ2.31 (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^+).

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 $ZnCl_2$ (150 mg, 1.1 mmol). The residue was purified by column chromatography (benzene). **5a**: Yield 76%; mp. 120-121 °C; ^{1}H NMR ($CDCl_3$) δ2.36 (s, 3H), 2.47 (s, 3H), 6.02 (s, 2H), 6.83-7.89 (m, 6H); IR (KBr) 2979, 2779, 1498, 1360, 1267, 1227, 1105, 1039 cm^{-1}; MS: m/z 298 (M^+). **5b**: Yield 88%; mp. 115-116 °C; ^{1}H NMR ($CDCl_3$)δ1.31 (t, 3H, J=7.1Hz), 2.37 (s, 3H), 2.79 (q, 2H, J=7.1Hz), 6.03 (s, 2H), 6.84-7.90 (m, 6H); IR (KBr) 2954, 2904, 1498, 1441, 1281, 1037 cm^{-1}; MS: m/z 312 (M^+). **5c**: Yield 93%; mp. 92-93 °C; ^{1}H NMR ($CDCl_3$)δ1.33 (d, 6H, J=7.02Hz), 2.36 (s, 3H), 2.83-3.18 (m, 1H), 6.02 (s, 2H), 6.83-7.85 (m, 6H); IR (KBr) 2939, 2906, 1496, 1441, 1288, 1037 cm^{-1}; MS: m/z 326 (M^+). **5d**: liquid; Yield 89%; ^{1}H NMR($CDCl_3$)δ1.42 (s, 9H), 2.37 (s, 3H), 6.03 (s, 2H), 6.98-7.85 (m, 6H); IR (neat) 2966, 2900, 1504, 1475, 1363, 1267, 1063 cm^{-1}; MS: m/z 340 (M^+). **5e**: Yield 82%; mp. 105-106 °C; ^{1}H NMR ($CDCl_3$)δ2.35 (s, 3H), 2.44 (s, 3H), 2.50 (s, 3H), 6.02 (s, 2H), 6.84-7.85 (m, 5H); IR (KBr) 2914, 1471, 1250, 1228, 1115, 1036 cm^{-1}; MS: m/z 312 (M^+). **5f**: Yield 50%; mp. 93-94 °C; ^{1}H NMR ($CDCl_3$)δ2.31 (s, 3H), 2.41

(s, 3H), 2.83 (s, 3H), 6.01 (s, 2H), 6.82-7.83 (m, 5H); IR (KBr) 2947, 1502, 1444, 1255, 1234, 1037 cm^{-1}; MS: m/z 312 (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), and the mixture was heated at 60-70 °C for 1h. 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 **6**. **6a**: Yield 86%; mp. 129-130 °C; ^1H NMR ($CDCl_3$)δ2.44 (s, 3H), 6.72-8.21 (m, 9H); IR (KBr) 3013, 2914, 1466, 1266, 1199, 1039 cm^{-1}; MS: m/z 208 (M^+). **6b:** Yield 81%; mp. 76-77 °C; ^1H NMR($CDCl_3$)δ1.28 (t, 3H, J=7.6Hz), 2.75 (q, 2H, J=7.6Hz), 6.95-7.87 (m, 9H); IR (KBr) 2959, 1560, 1467, 1267, 1038, cm^{-1}; MS: m/z 224 (M^+). **6c:** Yield 81%; mp. 87-88 °C; ^1H NMR ($CDCl_3$)δ1.31 (d, 6H, J=7.0Hz), 2.78-3.25 (m, 1H), 6.97-7.94 (m, 9H); IR (KBr) 2957, 1468, 1259, 1160, 1020 cm^{-1}; MS: m/z 236 (M^+). **6d:** Yield 82%; mp. 105-107 °C; ^1H NMR ($CDCl_3$)δ1.39 (s, 9H), 6.97-8.0 (m, 9H); IR (KBr) 2957, 1560, 1474, 1363, 1277, 1164, 1021 cm^{-1}; MS: m/z 250 (M^+). **6e:** Yield 78%; mp. 69-70 °C; ^1H NMR ($CDCl_3$) δ2.40 (s, 3H), 2.54 (s, 3H), 6.92-7.82 (m, 8H); IR (KBr) 2913, 1460, 1205, 1039, 1020 cm^{-1}; MS: m/z 222 (M^+). **6f:** liquid; Yield 74%; ^1H NMR ($CDCl_3$)δ2.43 (s, 3H), 2.50 (s, 3H), 6.85-7.93 (m, 8H); IR (neat) 2917, 2858, 1619, 1446, 1295, 1128, 1038 cm^{-1}; MS: m/z 222 (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; ^1H NMR ($CDCl_3$)δ2.43 (s, 3H), 6.01 (s, 2H), 6.79-7.45 (m, 7H); IR (KBr) 2897, 1462, 1230, 1200, 1107, 1037 cm^{-1}; MS: m/z 252 (M^+). **7b:** Yield 86%; mp. 99-100 °C; ^1H NMR ($CDCl_3$)δ1.27 (t, 3H, J=7.6Hz), 2.79 (q, 2H, J=7.6Hz), 6.00 (s, 2H), 6.79-7.45 (m, 7H); IR (KBr) 2958, 1500, 1466, 1284, 1234, 1103, 1037 cm^{-1}; MS: m/z 266 (M^+). **7c:** Yield 90%; mp. 113-114 °C; ^1H NMR ($CDCl_3$)δ1.30 (d, 6H, J=7.0Hz), 2.77-3.12 (m, 1H), 6.0 (s, 2H), 6.80-7.31 (m, 7H); IR (KBr) 2954, 2889, 1489, 1362, 1234, 1161, 1041 cm^{-1}; MS: (m/z) 280[M^-]. **7d:** Yield 84%; mp. 127-128 °C; ^1H NMR ($CDCl_3$)δ1.38 (s, 9H), 6.01 (s, 2H), 6.82-7.55 (m, 7H); IR (KBr) 2958, 2900, 1473, 1362, 1234, 1041 cm^{-1}; MS: m/z 294 (M^+). **7e:** Yield 97%; mp. 121-122 °C; ^1H NMR ($CDCl_3$)δ2.39 (s, 3H), 2.51 (s, 3H), 6.00 (s, 2H), 6.77-7.32 (m, 6H); IR (KBr) 2910, 1564, 1495, 1284, 1234, 1045 cm^{-1}; MS: m/z 266 (M^+). **7f:** Yield 93%; mp. 107-108 °C; ^1H NMR ($CDCl_3$)δ2.42 (s, 3H), 2.46 (s, 3H), 5.98 (s, 2H), 6.81-7.42 (m, 6H); IR (KBr) 2883, 1500, 1481, 1458, 1252, 1107 cm^{-1}; MS: m/z 266 (M^+).

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