Synthesis of 2-Methylbenzofuran Derivatives by Mean of Pummerer Reaction of Substituted Phenols with α-(Methylsulfinyl)acetone

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Recently we reported an extended application of 1-acyl-1-thioarboxebonents for a facile synthesis of 2-substituted benzofuran ring such as 2-methylbenzofuran derivatives and 2-arylbenezofuran derivatives from substituted phenols with 1-chloro-1-(methylthio)acetone under Friedel-Crafts reaction condition.

As a subsequent part of our program directed to develop the rapid construction of the basic skeleton of 2-substituted benzofuran, we became of interest in Pummerer rearrangement utilizing β-ketosulfoxides as the source for generation of 1-acyl-1-thioarboxebonent intermediates. Among the several examples of electrophilic aromatic substitution involving Pummerer reaction intermediates, there is well known the intramolecular version for the construction of a six-membered carboxycles and six or seven-membered heterocycles.

The present paper describes a novel one-step synthesis of 2-methylbenzofuran derivatives by Pummerer reaction of α-(methylsulfinyl)acetone (1) with substituted phenols in the presence of p-toluenesulfonic acid. A key step for the formation of this 2-methylbenzofuran ring 2 is the intermolecular nucleophilic attack of an aromatic ring on the 1-acyl-1-thioarboxebonent (1a) derived from the β-ketosulfoxide 1 in the presence of p-toluenesulfonic acid and successive dehydrocyclization.

Oxidation of α-(methylthio)acetone with sodium metaperiodate gave the compound 1 in 81% yield. As shown in Scheme 1, we have found that the intermolecular reaction of p-cresol and β-ketosulfoxide 1 efficiently takes place in the presence of two equivalents of anhydrous p-toluenesulfonic acid with continuous removal of the water produced during the reaction to afford 2,5-di-(methylthio)benzofuran (2a) in 63% yield. When the reaction was carried out with three equivalents of anhydrous p-toluenesulfonic acid without a Dean-Stark water separator, the compound 2a was obtained in 65% yield. This may suggest that the excess amounts of p-toluenesulfonic acid hold the water formed during the reaction.

Scheme 1. Reagent and condition: (i) p-TsOH, ClCH₂CH₃Cl, reflux, 1 h.
The Pummerer reaction of 1 or 2-phenol with 1 gave the corresponding 2-methyl-3-(methylthio)benzofuran derivatives 2bd in good yields. The reaction of p-chlorophenol with 1 furnished 5-chloro-2-methyl-3-(methylthio)benzofuran (2e) in 42% yield under the same condition. The low yield of this case may be explained by the lower nucleophilicity of the aromatic nuclei of p-chlorophenol than p-alkylphenol. Similarly, the treatment of disubstituted phenols with 1 in the presence of anhydrous p-toluenesulfonic acid gave the corresponding 2-methyl-3-(methylthio)benzofuran derivatives 2f-h.

Finally, the Pummerer reaction of 1 or 2-phenol derivatives with 1 was carried out under the same condition as the preparation of 2. 2-Methyl-3-(methylthio)phenol[1,2-b]furan (3) and 2-methyl-1-(methylthio)phenol[2,1-b]furan (4) were prepared from 1-phenol and 2-phenol in 43% and 65% yields, respectively.

The mp, IR and 1H NMR data of the adducts (2,3,4) obtained from the above Pummerer reaction were in good agreement with those reported by our previous work^1 on synthesis of 2-methyl-3-(methylthio)benzofurans under Friedel-Crafts condition.

In conclusion, a new and simple route for the construction of 2-methylbenzofuran ring could be established by the reaction of various substituted phenols with 1-nevl-1-thicarbocyclic intermediate 1a generated from β-ketosulfoxide 1 in the presence of anhydrous p-toluene-sulfonic acid. This Pummerer reaction would also afford a useful synthetic way to the 2-methylbenzofurans through reductive desulfurization of the methylthio group of 2.

In order to accomplish the feasibility for the synthetic methods of 2-alkyl or 2-arylbenzofuran ring using this Pummerer reaction, now the examination on the reactivity of substituted phenols with α-(methylsulfinyl)methyl alkyl or aryl ketones instead of methyl carbonyl group in β-ketosulfoxide 1 is in progress.

**EXPERIMENTAL**

Melting point was determined by a Gallenkamp melting point apparatus and is uncorrected. IR spectra were recorded on a JASCO FT-IR-3001 spectrometer. 1H NMR spectra were recorded on a Hitachi R-1500 FT NMR (60 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectrum was determined at 70 eV with a Hewlett Packard 5970 GC MS system by electron impact (EI) method. Silica gel (70-230 mesh, E. Merck) was used for column chromatography.

**Anhydrous p-toluenesulfonic Acid.** A solution of p-toluenesulfonic acid monohydrate (36 g) in benzene (200 mL) was refluxed for 10 h with continuous removal of the water produced by means of a Dean-Stark water separator under nitrogen atmosphere, then cooled. The solvent was evaporated off and the residual benzene was removed by high vacuum pump for 10 h. The crude anhydrous p-toluenesulfonic acid was used for the next reaction without further purification.

**α-(Methylsulfinyl)acetone (1).** A solution of sodium metaperiodate (6.42 g, 30 mmol) dissolved in water (60 mL) was added dropwise to a stirred solution of α-(methylsulfinyl)acetone (3.01 g, 29 mmol) in methanol (50 mL) at 0°C and the mixture is further stirred overnight at room temperature. Inorganic materials were removed by filtration, and the filtrate was extracted with chloroform (3 × 20 mL). The combined extracts were dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was chromatographed on silica gel using acetone as an eluent to give 1 (2.82 g, 81%) as a colorless oil. IR (neat) 2999, 2899, 1711 (C=O), 1422, 1356, 1300, 1253, 1167, 1055 (S=O) cm⁻¹. 1H NMR (CDCl₃) 82.35 (s, CH₃, 3H), 2.69 (s, CH₃, 3H), 3.74 and 3.79 (s, CH₃, 2H); MS (m/z) 120 [M⁺], 107, 90, 78, 63.
General procedure for the Synthesis of 2-Methyl-3-(methylthio)benzofurans (2). A solution of a substituted phenol (1.67 mmol), the sulfide 1 (200 mg, 1.67 mmol) and anhydrous p-toluenesulfonic acid (5 mmol) in 1,2-dichloroethane (10 mL) was heated under reflux for 1 h. The reaction mixture was washed with water (2 x 10 mL) to remove p-toluenesulfonic acid. The organic layer was dried over anhydrous MgSO4, and the solvent was evaporated off. The residue was purified by column chromatography (hexane:ethyl acetate, 15:1) to give 2.

2.5-Dimethyl-3-(methylthio)benzofuran (2a). A colorless oil. Yield 65% (208 mg); IR (neat) 2911, 1588, 1477, 1378, 1255, 1200, 1167, 1066 cm⁻¹; ¹H NMR (CDCl₃) δ 8.28 (s, CH₂), 7.65 Hz, 3H), 2.31 (s, CH₃), 2.52 (s, CH₃, 3H), 2.76 (q, CH₂CH₃, J=7.67 Hz, 2H), 6.93-7.60 (m, Ar-H, 3H).

5-Ethyl-2-methyl-3-(methylthio)benzofuran (2b). A colorless oil. Yield 66% (227 mg); IR (neat) 2963, 2931, 1474, 1425, 1380, 1233 cm⁻¹; ¹H NMR (CDCl₃) δ / (s, CH₂), J=7.65 Hz, 3H), 2.31 (s, CH₃), 2.52 (s, CH₃, 3H), 2.76 (q, CH₂CH₃, J=7.67 Hz, 2H), 6.93-7.60 (m, Ar-H, 3H).

5-Isopropyl-2-methyl-3-(methylthio)benzofuran (2c). A colorless oil. Yield 64% (235 mg); IR (neat) 2959, 2922, 2869, 1586, 1472, 1430, 1380, 1362, 1251, 1197, 1176 cm⁻¹; ¹H NMR (CDCl₃) δ 8.31 [d, (CH₂)₂CH₃], J=7.01 Hz, 6H], 2.31 (s, CH₃), 2.53 (s, CH₃, 3H), 2.69-3.27 [m, (CH₂)₂CH₃, 1H], 6.94-7.53 (m, Ar-H, 3H).

5-tert-Butyl-2-methyl-3-(methylthio)benzofuran (2d). A colorless oil. Yield 71% (278 mg); IR (neat) 2962, 2921, 2869, 1586, 1477, 1434, 1377, 1363, 1260, 1187, 1126, 1095, 1062; ¹H NMR (CDCl₃) δ 1.40 [s, (CH₃), 9H], 2.31 (s, CH₃), 2.53 (s, CH₃, 3H), 7.33 (s, Ar-H, 2H), 7.56 (s, Ar-H, 1H).

5-Chloro-2-methyl-3-(methylthio)benzofuran (2e). A colorless oil. Yield 42% (150 mg); IR (neat) 2990, 2921, 1382, 1444, 1255, 1183, 1081, 1051; ¹H NMR (CDCl₃) δ 8.30 (s, CH₃), 2.34 (s, CH₃, 3H), 7.28 (s, Ar-H, 2H), 7.57 (s, Ar-H, 1H).

5-Chloro-2-methyl-3-(methylthio)benzofuran (2e). A colorless oil. Yield 42% (150 mg); IR (neat) 2990, 2921, 1382, 1444, 1255, 1183, 1081, 1051; ¹H NMR (CDCl₃) δ 8.28 (s, CH₃), 2.43 (s, CH₃, 3H), 2.52 (s, CH₃, 3H), 6.87 (s, Ar-H, 1H), 7.20 (s, Ar-H, 1H).

2,4,6-Trimethyl-3-(methylthio)benzofuran (2g). A colorless oil. Yield 46% (158 mg); IR (neat) 2919, 1588, 1444, 1291, 1241, 1208, 1061, ¹H NMR (CDCl₃) δ 8.26 (s, CH₃, 3H), 2.41 (s, CH₃, 3H), 2.52 (s, CH₃, 3H), 2.76 (s, CH₃, 3H), 6.81 (s, Ar-H, 1H), 7.04 (s, Ar-H, 1H).

5-Chloro-2,7-dimethyl-3-(methylthio)benzofuran (2h). A colorless oil. Yield 50% (190 mg); IR (neat) 2988, 2922, 1384, 1457, 1336, 1302, 1276, 1229, 1185, 1119, 1048, ¹H NMR (CDCl₃) δ 8.29 (s, CH₃, 3H), 2.45 (s, CH₃, 3H), 2.54 (s, CH₃, 3H), 7.03 (s, Ar-H, 1H), 7.37 (s, Ar-H, 1H).

2-Methyl-3-(methylthio)naphtho[1,2-b]furan (3). By the same procedure for the preparation of 2, compound 3 was obtained from 1-naphthol (480 mg, 3.34 mmol) and sulfide 1 (401 mg, 3.34 mmol) in 43% yield; 128 mg as a colorless oil; IR (neat) 3060, 1757, 1520, 1434, 1376, 1315, 1273, 1241, 1170, 1042, 1074; ¹H NMR (CDCl₃) δ 8.34 (s, CH₃, 3H), 2.65 (s, CH₃, 3H), 7.20-8.41 (m, Ar-H, 6H).

2-Methyl-1-(methylthio)naphtho[2,1-b]furan (4). By the same procedure for the preparation of 2, compound 4 was obtained from 2-naphthol (480 mg, 3.34 mmol) and sulfide 1 (401 mg, 3.34 mmol) in 65% yield (495 mg) as a white solid; mp 78-79 °C (lit. mp 77-78 °C); IR (KBr) 3060, 2916, 1637, 1575, 1431, 1375, 1272; ¹H NMR (CDCl₃) δ 8.36 (s, CH₃, 3H), 2.64 (s, CH₃, 3H), 7.10-9.48 (m, Ar-H, 6H).

REFERENCES