Journal of the Korean Chemical Society
2001, *Vol. 45, No. 3*
Printed in the Republic of Korea

단 신

α-(메틸술피닐)아세톤과 치환페놀류의 Pummerer 반응에 의한 2-메틸벤조푸란 유도체의 합성

崔洪大*・徐弼子
동의대학교 자연과학대학 화학과
(2001. 2. 7 접수)

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

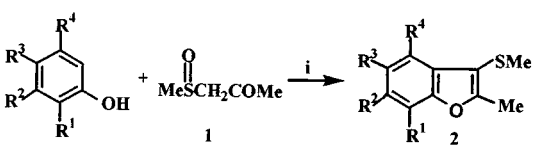
Hong-Dae Choi* and Pil-Ja Seo
Department of Chemistry, Dongeui University, Pusan 614-714, Korea
(Received February 7, 2001)

Recently we reported an extended application of 1-acyl-1-thiocarbocations for a facile synthesis of 2-substituted benzofuran ring such as 2-methylbenzofuran derivatives[1] and 2-arylbenzofuran derivatives[2] from substituted phenols with 1-chloro-1-(methylthio)ketones 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-thiocarbocationic 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 carbocycles[3,4] and six or seven-membered heterocycles.[5,6]

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-thiocarbocation (**1a**) derived from the β-ketosulfoxide **1** in the presence of *p*-toluenesulfonic acid and successive dehydrocyclization.

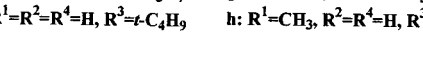
Oxidation of α-(methylthio)acetone with sodium metaperiodate gave the compound **1** in 81% yield. As shown in *Scheme* 1, we have found that the intermolecular reaction of *p*-cresol and β-ketosulfoxide **1** efficiently takes place in the presence of two equivalents of anhydrous *p*-toluenesulfonic acid with continuous removal of the water produced during the reaction to afford 2,5-di-methyl-3-(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.



1 **2**

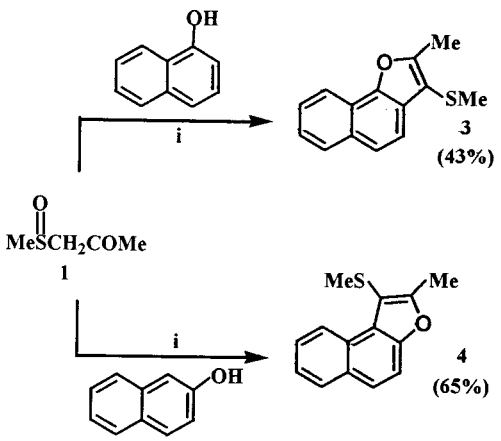
2a: 65% **2e: 42%**
2b: 66% **2f: 48%**
2c: 64% **2g: 46%**
2d: 71% **2h: 50%**

a: $R^1=R^2=R^4=H$, $R^3=CH_3$ **e:** $R^1=R^2=R^4=H$, $R^3=Cl$
b: $R^1=R^2=R^4=H$, $R^3=C_2H_5$ **f:** $R^1=R^3=CH_3$, $R^2=R^4=H$
c: $R^1=R^2=R^4=H$, $R^3=i\text{-}C_3H_7$ **g:** $R^1=R^3=H$, $R^2=R^4=CH_3$
d: $R^1=R^2=R^4=H$, $R^3=t\text{-}C_4H_9$ **h:** $R^1=CH_3$, $R^2=R^4=H$, $R^3=Cl$



1a

Scheme 1. Reagent and condition: (i) *p*-TsOH, $ClCH_2CH_2Cl$, reflux, 1 h.



Scheme 2. Reagent and condition: (i) *p*-TsOH, $ClCH_2CH_2Cl$, reflux, 1 h.

Thus, on heating under reflux with three equivalents of anhydrous *p*-toluenesulfonic acid in 1,2-dichloroethane for 1h, *p*-alkylphenols and β-ketosulfoxide **1** gave the corresponding 2-methyl-3-(methylthio)benzofuran derivatives **2b-d** 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)-naphthols with **1** was carried out under the same condition as the preparation of **2**. 2-Methyl-3-(methylthio)naphtho[1,2-*b*]furan (**3**) and 2-methyl-1-(methylthio)naphtho [2,1-*b*]furan (**4**) were prepared from 1-naphthol and 2-naphthol 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 agreements with those reported by our previous work[1] on synthesis of 2-methyl-3-(methylthio)benzofuans under Friedel-Crafts condition.

In conclusion, a new and simple route for construction of 2-methylbenzofuran ring could be established by the reaction of various substituted phenols with 1-acyl-1-thiocarbocationic intermediate **1a** generated from β-ketosulfoxide **1** in the presence of anhydrous *p*-toluenesulfonic 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 generality 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-300E 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 (30 g) in benzene (200 mL) was refluxed for 10h 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-(methylthio)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 $MgSO_4$, 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, 1233, 1167, 1055 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ2.35 (s, CH_3, 3H), 2.69 (s, CH_3, 3H), 3.74 and 3.79 (s, CH_2, 2H); MS (m/z) 120 [M^+], 107, 90, 78, 63

(base peak). 55.

General procedure for the Synthesis of 2-Methyl-3-(methylthio) benzofurans (2). A solution of a substituted phenol (1.67 mmol), the sulfoxide **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 × 10 mL) to remove *p*-toluenesulfonic acid. The organic layer was dried over anhydrous $MgSO_4$, 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 ($CDCl_3$) δ2.30 (s, CH_3, 3H), 2.45 (s, CH_3, 3H), 2.52 (s, CH_3, 3H), 6.86-7.55 (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, 1253 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.28 (t, CH_3CH_2, J=7.6Hz, 3H), 2.31 (s, CH_3, 3H), 2.52 (s, CH_3, 3H), 2.76 (q, CH_3CH_2, J=7.6Hz, 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, 1440, 1380, 1362, 1251, 1197, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.31 [d, $(CH_3)_2CH$, J=7.0Hz, 6H], 2.31 (s, CH_3, 3H), 2.53 (s, CH_3, 3H), 2.69-3.27 [m, $(CH_3)_2CH$, 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 ($CDCl_3$) δ1.40 [s, $(CH_3)_3$, 9H], 2.31 (s, CH_3, 3H), 2.53 (s, CH_3, 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, 1582, 1444, 1255, 1183, 1081, 1051; ^1H NMR ($CDCl_3$) δ2.30 (s, CH_3, 3H), 2.54 (s, CH_3, 3H), 7.28 (s, Ar-H, 2H), 7.57 (s, Ar-H, 1H).

2,5,7-Trimethyl-3-(methylthio)benzofuran (2f). A colorless oil; Yield 48% (165 mg); IR (neat) 2920, 1589, 1435, 1376, 1265, 1195, 1148, 1054; ^1H NMR ($CDCl_3$) δ2.29 (s, CH_3, 3H), 2.43 (s, CH_3, 2. 6H), 2.52 (s, CH_3, 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 ($CDCl_3$) δ2.26 (s, CH_3, 3H), 2.41 (s, CH_3, 3H), 2.52 (s, CH_3, 3H), 2.76 (s, CH_3, 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, 1584, 1457, 1436, 1402, 1376, 1315, 1262, 1229, 1185, 1119, 1048; ^1H NMR ($CDCl_3$) δ2.29 (s, CH_3, 3H), 2.45 (s, CH_3, 3H), 2.54 (s, CH_3, 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 sulfoxide **1** (401 mg, 3.34 mmol) in 43% yield (328 mg) as a colorless oil. IR (neat) 3060, 2919, 1577, 1520, 1434, 1376, 1315, 1273, 1241, 1170, 1102, 1074; ^1H NMR ($CDCl_3$) δ2.34 (s, CH_3, 3H), 2.65 (s, CH_3, 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 sulfoxide **1** (401 mg, 3.34 mmol) in 65% yield (495 mg) as a white solid. mp 78-79 °C (lit.[1b] mp 77-78 °C); IR (KBr) 3060, 2916, 1637, 1575, 1434, 1375, 1272; ^1H NMR ($CDCl_3$) δ2.36 (s, CH_3, 3H), 2.64 (s, CH_3, 3H), 7.10-9.48 (m, Ar-H, 6H).

REFERENCES

1. (a) Choi, H. D.; Seo, P. J.; Son, B. W. *J. Korean Chem. Soc.* **1998**, *42*, 719. (b) Choi, H. D.; Seo, P. J.; Son, B. W. *J. Korean Chem. Soc.* **1999**, *43*, 237.
2. (a) Choi, H. D.; Seo, P. J.; Son, B. W. *J. Korean Chem. Soc.* **1999**, *43*, 494. (b) Choi, H. D.; Seo, P. J.; Son, B. W. *J. Korean Chem. Soc.* **1999**, *43*, 606. (c) Seo, P. J.; Ha, M. C.; Choi, H. D.; Son, B. W. *J. Korean Chem. Soc.* **2000**, *44*, 391.
3. Oikawa, Y.; Yonemitsu, O. *Tetrahedron.* **1974**, *30*, 2653.
4. Blair, I. A.; Mander, L. N.; Mundil, P. H. C. *Aust. J. Chem.* **1981**, *34*, 1235.
5. Tamura, Y.; Choi, H. D.; Shindo, H.; Uenishi, J.; Ishibashi, H. *Tetrahedron Letters*, **1981**, *22*, 81.
6. Ishibashi, H.; Okada, M.; Akiyama, A.; Nomura, K.; Ikeda, M. *J. Heterocycl. Chem.* **1986**, *23*, 1163.