

## A New Route to *o*-Methylthiomethylated Phenols by Use of *S,S*-Dimethylsulfilimines

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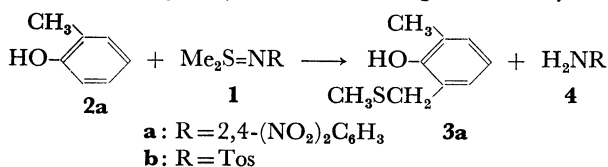
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**Synopsis.** As convenient intermediates to introduce methyl groups into the *o*-positions of phenols, *o*-methylthiomethylphenols (*o*-MTM-phenols) were prepared in high selectivity and moderate yield by the reaction of phenols with sulfilimines such as *S,S*-dimethyl-*N*-(2,4-dinitrophenyl)- and *S,S*-dimethyl-*N*-tosylsulfilimines.

Phenols having methyl groups at the position ortho to the hydroxyl group are useful intermediates in organic synthesis.

The *o*-methylthiomethylation (*o*-MTM-ation) of phenol followed by reduction is known, as an indirect method to introduce methyl groups into the position ortho to hydroxyl group in phenols. For *o*-MTM-ation, methods using dimethyl sulfoxide together with dicyclohexylcarbodiimide,<sup>1)</sup> acetic anhydride,<sup>2)</sup> or pyridine-SO<sub>3</sub>,<sup>3)</sup> and dimethyl sulfide with *N*-chlorosuccinimide<sup>4)</sup> have been reported. These methods have disadvantages such as low yield, minor selectivity, and trouble in handling.

We found that easily accessible sulfilimines, *S,S*-dimethyl-*N*-(2,4-dinitrophenyl)sulfilimine (**1a**) and *S,S*-dimethyl-*N*-tosylsulfilimine (**1b**), react with phenols to give the corresponding methylthiomethylated phenols, which are convertible into the corresponding methylated phenols,<sup>1c,4)</sup> in good yield and with high selectivity.



A mixture of *o*-cresol (**2a**) and a half equivalent of **1a** was heated in bulk at 120–130 °C for 3 h. Work-up of the reaction mixture gave 6-MTM-2-methylphenol (**3a**) in 95% yield. The NMR data of **3a** were identical with those in literature.<sup>1b)</sup> Similarly, from the reaction between **2a** and **1b** **3a** was obtained in 78% yield (based on reacted **1b**), which was found to be spectroscopically pure by NMR. In contrast with the former case, unreacted **1b** was conveniently recovered. The lower yield in the latter case might be caused by more difficult proton shift from **2a** to **1**.

A similar tendency was observed in the variation of methylthiomethylating agents, *N*-arylsulfonyl-*S,S*-dimethylsulfilimines (**1b**–**1e**) (Table 1): the sulfilimine having electron-donating group on benzene ring tends to give **3a** in a higher yield.

Although **1b** gives **3a** in a lower yield as compared with **1a**, the former is more accessible from dimethyl sulfide and chloramine T. The *o*-MTM-ation of other phenols with **1b** was examined. The corresponding *o*-MTM-phenols were obtained in a reasonable yield and with high selectivity at the position ortho to

TABLE 1. EFFECT OF SUBSTITUTENT ON THE YIELD OF **3a**

|           | Me <sub>2</sub> S=NSO <sub>2</sub> Ar   | Yield of <b>3a</b> (%) |
|-----------|---|------------------------|
| <b>1b</b> | Ar=4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>                                      | 50                     |
| <b>1c</b> | C <sub>6</sub> H <sub>5</sub>   | 39                     |
| <b>1d</b> | 4-ClC <sub>6</sub> H <sub>4</sub>   | 35                     |
| <b>1e</b> | 2,4,6-(CH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>                     | 62                     |
| <b>1a</b> | Me <sub>2</sub> S=NC <sub>6</sub> H <sub>3</sub> (NO <sub>2</sub> ) <sub>2</sub> (2, 4) | 95 <sup>a)</sup>       |

a) Isolated yield.

TABLE 2. *o*-MTM-ATION OF PHENOLS USING **1b**<sup>a)</sup>

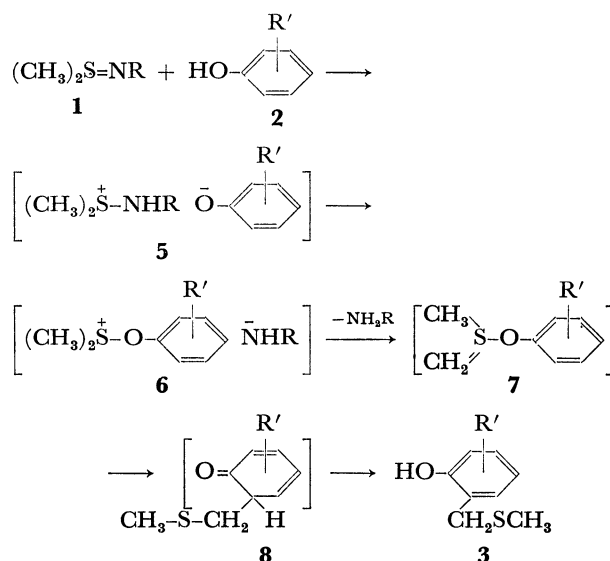
$$\text{HOAr} + \text{Me}_2\text{S}=\text{NTs} \longrightarrow \text{HOAr}'\text{-MTM-}(o) + \text{H}_2\text{NTs}$$

| <b>2</b>  | <b>1b</b> | <b>3</b>               | <b>4b</b>  |           |
|---|-----------|------------------------|--|-----------|
| <b>2</b>  |           | Y (%)                  | Bp (°C/Torr)   | Y (%)     |
| <b>a</b> 2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> OH                   | <b>a</b>  | 43 (73)                | 73/3 × 10 <sup>-2</sup><br>[70/10 <sup>-3</sup> ] <sup>1b)</sup> | 52 (≈100) |
| <b>b</b> 2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> OH                  | <b>b</b>  | 35 (78)                | 92–93/<br>3 × 10 <sup>-2</sup>                                   | 45 (≈100) |
| <b>c</b> 2,5-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> OH | <b>c</b>  | 69 (96)                | oil  | 72 (≈100) |
| <b>d</b> 3,5-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> OH | <b>d</b>  | 58 (58 <sup>b)</sup> ) | oil  | ≈100      |
| <b>e</b> 2,3,5-(CH <sub>3</sub> ) <sub>3</sub> CH <sub>2</sub> OH             | <b>e</b>  | 37 (64)                | oil  | 58 (≈100) |

a) Data in parentheses show the yields based on the reacted **1b**. b) Bis-TMM-phenol was obtained in 35% yield.

hydroxyl group (Table 2).

The reaction scheme, in which *o*-MTM-phenols are formed from **2** and **1**, can be described partly from Moffatt's mechanism.<sup>1)</sup> Especially in the first stage of the reaction, the proton shift (**2** to **1**), might play the most important role.



## Experimental

**Materials.** Chloramine T and chloramine B of reagent grade were used. Sodium salts of *N*-chloro-*p*-chlorobenzene-sulfonamide and *N*-chloromesitylenesulfonamide were prepared by the treatment of corresponding sulfonamides with aq solution of sodium hypochlorite (7%).

**Preparation of Sulfilimines.** **1a** was prepared by the method described in a previous paper.<sup>5)</sup> *N*-Arylsulfonyl-*S,S*-dimethylsulfilimines were prepared by the reaction of dimethyl sulfide with sodium salts of *N*-chloroarenesulfonamides.<sup>6)</sup> **1b.** Yield: 92%; Mp: 154—155 °C (MeOH) (lit,<sup>7)</sup> 154—155 °C). *N*-Phenylsulfonyl-*S,S*-dimethylsulfilimine (**1d**). Yield: 86%; Mp: 128—129 °C (MeOH) (lit,<sup>8)</sup> 131 °C). *N*-(*p*-Chlorophenylsulfonyl)-*S,S*-dimethylsulfilimine (**1d**). Yield: 80%; Mp: 115—116 °C (MeOH); IR(KBr): 1273 ( $\nu_{as}SO_2$ ), 1133 ( $\nu_s SO_2$ ), 958 (S=N), 820 cm<sup>-1</sup> (*p*-C<sub>6</sub>H<sub>4</sub>). Found: C, 37.97; H, 3.97; N, 5.57% (Calcd for C<sub>9</sub>H<sub>10</sub>ClNO<sub>2</sub>S<sub>2</sub>: C, 38.16; H, 4.01; N, 5.56%). *S,S*-Dimethyl-*N*-(2,4,6-trimethylphenylsulfonyl)sulfilimine (**1e**). Yield: 83%; Mp: 167—168.5 °C (MeOH); IR(KBr): 1280 ( $\nu_{as}SO_2$ ), 1134 ( $\nu_s SO_2$ ), 945 (S=N), 843 cm<sup>-1</sup> (*p*-C<sub>6</sub>H<sub>4</sub>). Found: C, 50.84; H, 6.69; N, 5.49% (Calcd for C<sub>11</sub>H<sub>7</sub>NO<sub>2</sub>S<sub>2</sub>: C, 50.93; H, 6.62; N, 5.40%).

**Reaction of 2 with 1.** **General Procedure:** A mixture of 10—20 mmol of **2** and a half equivalent of **1** was heated at 120—130 °C for 3—7 h. After the reaction, excess **2** was removed by distillation under reduced pressure. The resulting residues were extracted with hexane. The combined extracts were evaporated to dryness to give very viscous oils, which were almost pure *o*-MTM-phenols (**3**) as confirmed by NMR. The oils were purified by distillation (for **3a** and **3b**) or column chromatography (silica gel-hexane, for **3c**, **3d** and **3e**) for confirmation of the structures. 2,4-Dinitroaniline (**4a**), *p*-toluenesulfonamide (**4b**) and unreacted **1b** were separated from insoluble parts in hexane by extraction with ether and identified by comparison with authentic samples.

**Reaction of *o*-Cresol (2a) with 1:** (A) 1.08 g (10 mmol) of **2a** was reacted with 1.12 g (5 mmol) of **1a** at 120—130 °C for 3 h to give 798 mg (95%, based on **1a**) of **3a** and 914 mg of **4a**. (B) 1.08 g of **2a** was reacted with 1.16 g (5 mmol) of **1b** at 120—130 °C for 5 h to give 361 mg of **3a** and 445 mg of **4b**. **3a:** Bp: 73 °C (3 × 10<sup>-2</sup>) [lit,<sup>1b)</sup> 70 (10<sup>-3</sup>)]. IR(neat): 3400—3300 and 1210—1190 cm<sup>-1</sup> (OH). NMR (CDCl<sub>3</sub>):  $\delta$  1.96 (s, 3H), 2.26 (s, 3H), 3.75 (s, 2H), 6.62 (s, 1H), 6.7—7.3 (m, 3H).<sup>1b)</sup>

**Reaction of Guaiacol (2b) with 1b:** 2.48 g (20 mmol) of **2b** was reacted with 2.31 g (10 mmol) of **1b** at 120—130 °C for 5 h to give 644 mg of 6-MTM-2-methoxyphenol (**3b**) and 770 mg of **4b**. **3b:** Bp: 92—93 °C (3 × 10<sup>-2</sup>). IR (neat): 3500—3400 and 1220 (OH), 1260 and 1070 cm<sup>-1</sup> (C—O—C). NMR (CDCl<sub>3</sub>):  $\delta$  2.08 (s, 3H), 3.75 (s, 2H), 3.89 (s, 3H), 5.92 (s, 1H), 6.7—7.0 (m, 3H).<sup>2a)</sup> (Found: C, 58.48; H,

6.73; S, 17.12%. Calcd for C<sub>9</sub>H<sub>12</sub>O<sub>2</sub>S: C, 58.66; H, 6.58; S, 17.40%.)

**Reaction of 2,5-Dimethylphenol (2c) with 1b:** 2.44 g (20 mmol) of **2c** was reacted with 2.31 g of **1b** at 120—130 °C for 7 h to give 1.25 g of 6-MTM-2,5-dimethylphenol (**3c**) and 1.23 g of **4b**. **3c:** IR (neat): 3500—3400 and 1220 cm<sup>-1</sup> (OH). NMR (CCl<sub>4</sub>):  $\delta$  1.96 (s, 3H), 2.18 (s, 3H), 2.27 (s, 3H), 3.72 (s, 2H), 6.17 (s, 1H), 6.54 (d, 2H), 6.86 (d, 2H).<sup>1b)</sup> MS: *m/e* 182 (M<sup>+</sup>).

**Reaction of 3,5-Dimethylphenol (2d) with 1b:** 2.44 g (20 mmol) of **2d** was reacted with 2.31 g of **1b** at 120—130 °C for 7 h to give 1.06 g of 6-MTM-3,5-dimethylphenol (**3d**) and 1.70 g of **4b**. **3d:** IR (neat): 3400 and 1150 (OH), 830 cm<sup>-1</sup> (C<sub>6</sub>H<sub>2</sub>). NMR (CCl<sub>4</sub>):  $\delta$  1.99 (s, 3H), 2.22 (s, 3H), 2.29 (s, 3H), 3.72 (s, 2H), 6.17 (s, 1H), 6.33 (s, 1H), 6.54 (s, 1H). MS: *m/e* 182 (M<sup>+</sup>).

**Reaction of 2,3,5-Trimethylphenol (2e) with 1b:** 2.72 g (20 mmol) of **2e** was reacted with 2.31 g of **1b** at 120—130 °C for 7 h to give 726 mg of 6-MTM-2,3,5-trimethylphenol (**3e**) and 991 mg of **4b**. **3e:** IR (neat): 3400—3350 and 1140 cm<sup>-1</sup> (OH). NMR (CCl<sub>4</sub>):  $\delta$  1.97 (s, 3H), 2.12 (s, 3H), 2.25 (s, 3H), 3.75 (s, 2H), 6.22 (s, 1H), 6.47 (s, 1H). Found: C, 66.95; H, 8.08%. Calcd for C<sub>11</sub>H<sub>16</sub>OS: C, 67.29; H, 8.23%.

**Effect of Substituents on the Yield of 3a:** Reactions of 2 mmol of **2a** with 1 mmol of **1** (**b—c**) were carried out at 130 °C for 5 h without solvent. Excess **2a** was removed from the reaction mixtures by distillation *in vacuo*. The residues obtained were analyzed for **3a** by liquid chromatography (a Shimadzu High Speed Chromatograph 840, Permaphase ODS-50% MeOH-H<sub>2</sub>O) after evaporation of hexane. The data obtained (yield of **3a**) are given in Table 1.

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