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

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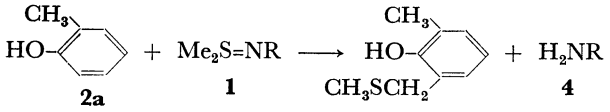
Synopsis. As convenient intermediates to introduce methyl groups into the *o*-positions of phenols, *o*-methylthiomethylphenols (*o*-MTM-phenols) were prepared in high selectivity and moderate yield by the reaction of phenols with sulfilimines such as *S,S*-dimethyl-*N*-(2,4-dinitrophenyl)- and *S,S*-dimethyl-*N*-tosylsulfilimines.

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,[1] acetic anhydride,[2] or pyridine–SO_3,[3] and dimethyl sulfide with *N*-chlorosuccinimide[4] 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,[1c,4] in good yield and with high selectivity.



2a **1** **3a** **4**

a: R=2,4-$(NO_2)_2C_6H_3$
b: R=Tos

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.[1b] 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 hydroxyl group (Table 2).

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

	$Me_2S{=}NSO_2Ar$	Yield of **3a** (%)
1b	Ar=4-$CH_3C_6H_4$	50
1c	C_6H_5	39
1d	4-ClC_6H_4	35
1e	2,4,6-$(CH_3)_3C_6H_2$	62
1a	$Me_2S{=}NC_6H_3(NO_2)_2$(2, 4)	95[a]

a) Isolated yield.

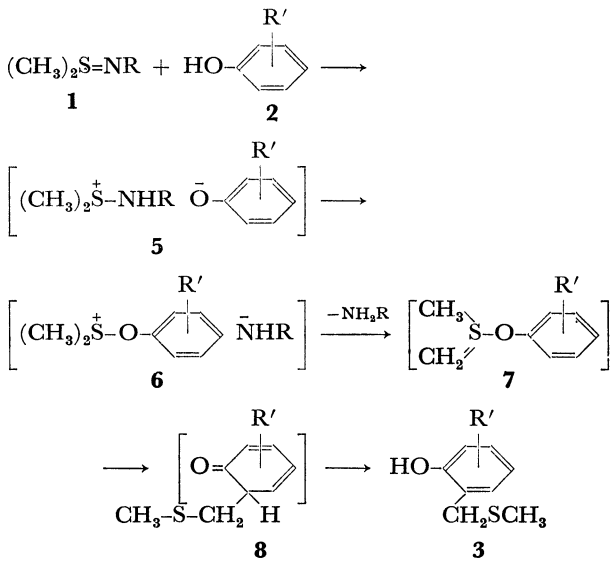
TABLE 2. *o*-MTM-ATION OF PHENOLS USING **1b**[a]

$HOAr + Me_2S{=}NTs \longrightarrow HOAr'\text{-}MTM\text{-}(o) + H_2NTs$
2 **1b** **3** **4b**

2	**3** Y (%)	**3** Bp (°C/Torr)	**4b** Y (%)
a 2-$CH_3C_6H_4OH$	**a** 43 (73)	73/3×10^{-2} [70/10^{-3}][1b]	52 (≈100)
b 2-$CH_3OC_6H_4OH$	**b** 35 (78)	92—93/ 3×10^{-2}	45 (≈100)
c 2,5-$(CH_3)_2C_6H_3OH$	**c** 69 (96)	oil	72 (≈100)
d 3,5-$(CH_3)_2C_6H_3OH$	**d** 58 (58)[b]	oil	≈100
e 2,3,5-$(CH_3)_3CH_2OH$	**e** 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.

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



1 **2** **5** **6** **7** **8** **3**

Experimental

Materials. Chloramine T and chloramine B of reagent grade were used. Sodium salts of *N*-chloro-*p*-chlorobenzenesulfonamide 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.[5] *N*-Arylsulfonyl-*S,S*-dimethylsulfilimines were prepared by the reaction of dimethyl sulfide with sodium salts of *N*-chloroarenesulfonamides.[6] **1b.** Yield: 92%; Mp: 154—155 °C (MeOH) (lit,[7] 154—155 °C). *N*-Phenylsulfonyl-*S,S*-dimethylsulfilimine (**1d**). Yield: 86%; Mp: 128—129 °C (MeOH) (lit,[8] 131 °C). *N*-(*p*-Chlorophenylsulfonyl)-*S,S*-dimethylsulfilimine (**1d**). Yield: 80%; Mp: 115—116 °C (MeOH); IR(KBr): 1273 ($\nu_{as}SO_2$), 1133 (ν_s SO_2), 958 (S=N), 820 cm^{-1} (*p*-C_6H_4). Found: C, 37.97; H, 3.97; N, 5.57% (Calcd for $C_8H_{10}ClNO_2S_2$: 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 (ν_sSO_2), 945 (S=N), 843 cm^{-1} (*p*-C_6H_4). Found: C, 50.84; H, 6.69; N, 5.49% (Calcd for $C_{11}H_7NO_2S_2$: 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^{-2}) [lit,[1b] 70 (10^{-3})]. IR(neat): 3400—3300 and 1210—1190 cm^{-1} (OH). NMR ($CDCl_3$): δ 1.96 (s, 3H), 2.26 (s, 3H), 3.75 (s, 2H), 6.62 (s, 1H), 6.7—7.3 (m, 3H).[1b]

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 5h to give 644 mg of 6-MTM-2-methoxyphenol (**3b**) and 770 mg of **4b**. **3b**; Bp: 92—93 °C (3×10^{-2}). IR (neat): 3500—3400 and 1220 (OH), 1260 and 1070 cm^{-1} (C–O–C). NMR ($CDCl_3$): δ 2.08 (s, 3H), 3.75 (s, 2H), 3.89 (s, 3H), 5.92 (s, 1H), 6.7—7.0 (m, 3H).[2a] (Found: C, 58.48; H, 6.73; S, 17.12%. Calcd for $C_9H_{12}O_2S$: 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^{-1} (OH). NMR (CCl_4): δ 1.96 (s, 3H), 2.18 (s, 3H), 2.27 (s, 3H), 3.72 (s, 2H), 6.17 (s, 1H), 6.54 (d, 2 H), 6.86 (d, 2H).[1b] MS: *m/e* 182 (M^+).

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 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^{-1} (C_6H_2). NMR (CCl_4): δ 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^+).

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 and1140 cm^{-1} (OH). NMR (CCl_4): δ 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 $C_{11}H_{16}OS$: 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_2O) after evaporation of hexane. The data obtained (yield of **3a**) are given in Table 1.

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