

THE ORTHO-ALKYLATION OF PHENOLS

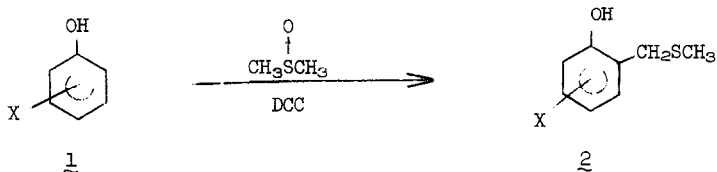
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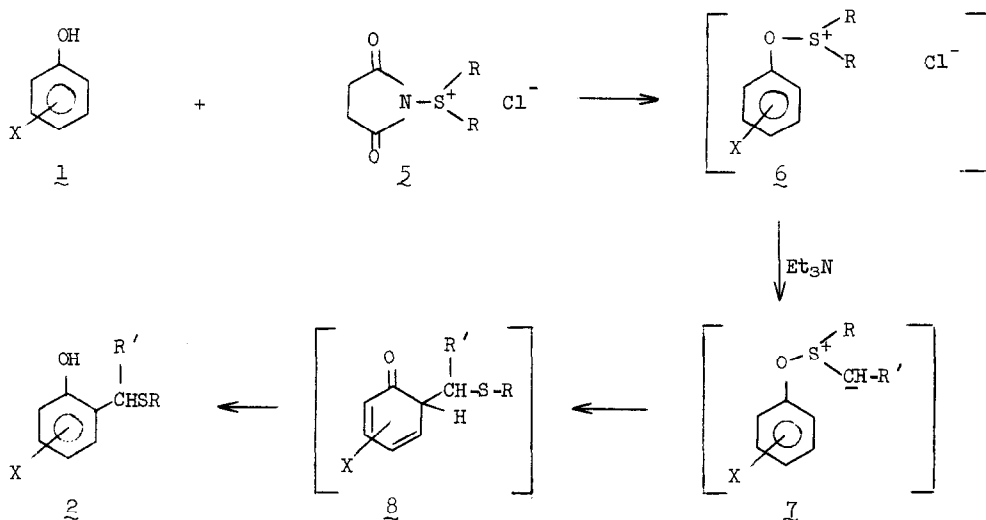
The conversion of phenols (1) into *o*-methylthiomethylphenols (2) on attempted Moffatt oxidation<sup>2</sup> with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) was first reported in 1965.<sup>3</sup> Subsequently, the reaction of 1 with dimethyl sulfoxide to give 2 has



been achieved in the presence of (a) DCC and pyridinium trifluoroacetate,<sup>3,4</sup> (b) pyridine-sulfur trioxide,<sup>5</sup> (c) acetic anhydride,<sup>6</sup> and (d) by extensive heating.<sup>7</sup> The procedures which utilized DCC were complicated by the necessity of separating the products from relatively large amounts of dicyclohexylurea, while the other modifications often gave unimpressive yields. Subsequently, the *o*-methylthiomethylphenols could be reductively desulfurized to produce the simple *o*-alkylphenols.


We now wish to report a new method for the synthesis of ortho-alkylated phenols from phenols and dialkyl sulfides. The process involves the reaction of *N*-chlorosuccinimide (3) with a dialkyl sulfide, 4, to give an azasulfonium salt,<sup>8,9</sup> 5. When phenol is added to a methylene chloride solution of 5 an intermediate is formed, which has been assigned structure 6 on the basis of mechanistic considerations. Treatment of 6 with a base, such as triethylamine, should give the ylide 7, which would be expected to yield the dienone 8 via a Sommelet-Hauser type rearrangement.<sup>3-7,10</sup> Proton transfer and accompanying rearomatization would then produce the *o*-methylthiomethylphenol, 2.

In the general procedure, 0.40 mole of *N*-chlorosuccinimide (3) in 2 liters of dry methylene chloride was combined with 0.50 mole of dialkyl sulfide at 0 to -5<sup>o</sup> to give the



azasulfonium salt, 5. The temperature was lowered to  $-25^\circ$  and 0.8 mole of a suitable phenol, 1, in 100 ml of methylene chloride was added over a 15-min period. The reaction mixture was stirred for 30 min, 0.41 mole of triethylamine was added at  $-25^\circ$ , and the reaction mixture was allowed to warm slowly to room temperature. Removal of the solvent and salts, and distillation of the residue gave the o-methylthiomethylphenol, 2, and also permitted recovery of any unreacted phenol.<sup>11</sup> Table 1 lists the yields obtained in these reactions based on unrecovered phenol. Also included in Table 1 are the yields obtained in the reductive desulfurization of the methylthiomethylated phenols to the simple alkylated phenol. The potential of the process is illustrated by the last example in the table in which tetrahydrothiophene

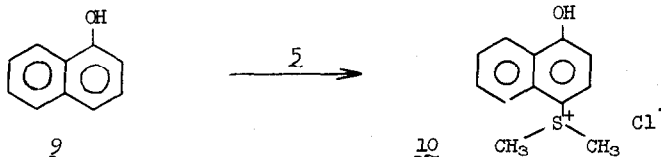
**Table 1.** Yields Obtained in the Methylthiomethylation of Phenols and Subsequent Raney-nickel Reductive Desulfurization.

 X	RSR		% Yield of <u>2</u> <sup>a</sup>	% Yield of o-Methylphenol Obtained on Desulfurization
	R	R		
H	$\text{CH}_3$	$\text{CH}_3$	58	95
p- $\text{CH}_3$	$\text{CH}_3$	$\text{CH}_3$	62	93
p- $\text{OCH}_3$	$\text{CH}_3$	$\text{CH}_3$	49	98
p-Cl	$\text{CH}_3$	$\text{CH}_3$	63	94
o- $\text{CH}_3$	$\text{CH}_3$	$\text{CH}_3$	62	93
o- $\text{CH}_3$	-( $\text{CH}_2$ ) <sub>4</sub> -		73	92 <sup>b</sup>

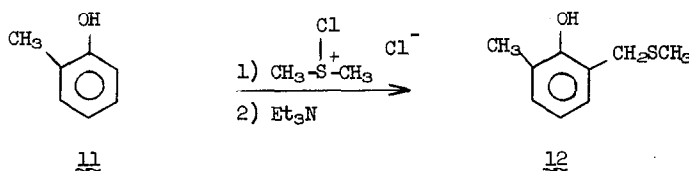
(a) Yields are based on unrecovered phenol. All yields represent material of greater than 97% purity. Satisfactory analytical data has been obtained on all new compounds. (b) The product in this case was 2-methyl-6-n-butylphenol.

is used as the sulfide. In this example the *o*-cresol was substituted with an *o*-*n*-butyl group in 67% overall yield.

Our findings contrast surprisingly with those of Vilsmaier and Sprügel, who reported<sup>9</sup> that 5 (R=R=CH<sub>3</sub>) reacted with  $\alpha$ -naphthol (9) to give the sulfonium salt 10. Apparently,



the dramatic difference between our observations and those reported are a result of the lower temperatures and added base utilized in our studies. In a related study, Claus and Rieder have reported<sup>12</sup> that dialkylchlorosulfonium chlorides react with phenols to give sulfonium salts analogous to 10 in high yield. In view of our observations on the reaction of 5 with phenols, we decided to reinvestigate the behavior of phenols in the presence of dialkylchlorosulfonium chlorides.<sup>13</sup> We have found that treatment of *o*-cresol (11) with dimethylchlorosulfonium chloride at  $-60^\circ$  followed by addition of triethylamine gave a 66% yield of 12



(73% based on unrecovered *o*-cresol). Again, it would appear that the lower temperatures and added base present in our studies constituted the basis for a major change in reaction pathway from that which had been previously observed.<sup>12</sup>

In summary, we have developed a new method for the specific ortho-alkylation of phenols which we feel is far superior to previously reported methods.

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