# Alkylmercaptophenols by Sulfenylation of Phenols

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Alkyl disulfides were found to react with phenols in the presence of acid catalysts to produce alkylmercaptophenols. Alkylmercaptophenols also were prepared by the reaction of alkanesulfenyl chlorides with phenols and by the hydrolysis of halothioanisoles.

Several methods for the preparation of alkylmercaptophenols were investigated owing to the utility of certain of these compounds in the synthesis of phosphorous esters possessing insecticidal activity.[1]

Phenols are known to react with alkyl disulfides in the presence of Lewis acids to form alkylmercaptophenols.[2] We have discovered that the reaction is catalyzed by protonic acids and by acidic ion-exchange resins. Thus in the presence of phosphoric or polyphosphoric acid, a refluxing and vigorously stirred solution of methyl disulfide and phenol yielded methylmercaptophenol with the evolution of methylmercaptan.

$$C_6H_5OH + CH_3SSCH_3 \xrightarrow[\text{Heat}]{H_3PO_4} CH_3SC_6H_4OH + CH_3SH$$

The synthesis is especially suitable for successive preparations of mercaptophenols since the catalyst layer is insoluble and can be withdrawn readily for re-use. In three successive runs using phenol and methyl disulfide, the first run gave a 47% yield of 4-methylmercaptophenol, while two subsequent runs using the recovered catalyst layer gave yields near 70%.

Cationic ion-exchange resins also catalyzed the formation of alkylmercaptophenols. For example, the efficiency of resin AG50-X12 (Bio-Rad Laboratories) was comparable to that of phosphoric acid, but the preparation was cumbersome owing to the large amounts of solvent necessary for complete elution of the products from the resin.

The phenol–disulfide reaction was catalyzed more efficiently by acids which were soluble in the reaction mixture. Thus alkanesulfonic acids and arenesulfonic acids caused a marked reduction in reaction time (from eight to twenty-four hours to one to two hours total reaction time) when compared to phosphoric acid. A large amount of tars was produced, which decreased conversions markedly. Catalysis by concentrated sulfuric acid required both a shorter reaction time and afforded higher yield of alkylmercaptophenols (Table I). Since phenols are sulfonated at the reaction temperatures employed[3] cocatalysis with phenolsulfonic acids formed during the reaction probably occurs. In the absence of catalysts, 4-methylmercaptophenol could not be detected even when the reaction of methyl disulfide and phenol was attempted in an autoclave at 300°.

A probable mechanism for the acid catalysis is that coordination of the catalyst by the disulfide occurs followed by cleavage of the sulfur–sulfur linkage and formation of a highly reactive sulfenium ion intermediate.[4] Electrophilic attack at the aromatic nucleus by the sulfenium ion follows to yield the mercaptophenol and regenerate the catalyst.

$$CH_3SSCH_3 + H^+ \longrightarrow (CH_3\overset{H}{\overset{|}{S}}SCH_3)^+ \longrightarrow CH_3SH + CH_3S^+$$

$$CH_3S^+ + C_6H_5OH \longrightarrow CH_3SC_6H_4OH + H^+$$

Several alkylmercaptophenols were prepared by the reaction of alkanesulfenyl chlorides with phenols.[5] Best yields were obtained when the alkanesulfenyl halides were used immediately after preparation since rapid deterioration of the halides occurred even at Dry Ice temperatures.[6] The reaction of methanesulfenyl bromide with phenol is the first such reaction reported for the unstable sulfenyl bromides (Table II).

Addition of zinc chloride or aluminum chloride to the reaction mixture did not catalyze the reaction but resulted in reduced yields of alkylmercaptophenols and the formation of what appears to be a high sulfur containing polymer probably resulting from the autocondensation of methanesulfenyl chloride. *para* Substituted phenols reacted with alkylsulfenyl chlorides

$$n\text{-}CH_3SCl \xrightarrow{AlCl_3} (CH_2S)_n$$

slowly to give at best very poor yields of alkylmercaptophenols, presumably due to steric hindrance at the *ortho* position.[7]

The reaction of alkanesulfenyl chlorides with phenols appears to be operative through a reactive sulfenium ion intermediate, $RS^+$, resulting from ionization of the sulfenyl chloride,[8] although a free-radical structure for the $CH_2S$ intermediate cannot be excluded.[9]

An alternate approach to the alkylmercaptophenols involved the hydrolysis of halothioanisoles.

In the presence of a copper–copper oxide catalyst the readily available 4-bromo- and 4-chlorothioanisoles were hydrolyzed readily to 4-methylmercaptophenol by aqueous sodium hydroxide solution at 225–300°. As expected the bromothioanisole was hydrolyzed more readily than the chloro compound (Table III). High yields were obtained with nearly quantitative recovery of unchanged thioanisole.

The physical and chemical properties of the known alkylmercaptophenols prepared by us were in agree-

(1) See, for example, T. R. Fukuto and R. L. Metcalf, *J. Agr. Food Chem.*, **4**, 930 (1956); R. L. Metcalf, "Organic Insecticides," Interscience Publishers, Inc., New York, N. Y., 1955, p. 251; R. D. O'Brien, "Toxic Phosphorous Esters, Chemistry, Metabolism and Biological Effects," Academic Press, New York, N. Y., 1960, and references cited therein.

(2) D. Delfs and K. Wedemeyer, U. S. Patent 2,923,743 (1960).

(3) F. Muth, "Methoden des Organischen Chemie," Vol. IX, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1955, p. 471.

(4) N. Kharasch, W. Krieg, and T. C. Bruice, *J. Am. Chem. Soc.*, **77**, 931 (1955); R. E. Benesch and R. Benesch, *ibid.*, **80**, 1666 (1958); W. King, A. J. Parker, and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(5) D. Delfs and K. Wedemeyer, U. S. Patent 2,995,608 (1961).

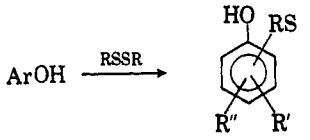
(6) I. B. Douglass, "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p. 350.

(7) N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 269 (1946).

(8) W. L. Orr and N. Kharasch, *J. Am. Chem. Soc.*, **75**, 6030 (1953).

(9) J. L. Franklin and H. E. Lumpkin, *ibid.*, **74**, 1024 (1952); V. Prey and E. Gutschik, *Monatsh. Chem.*, **90**, 551 (1959); V. Prey, E. Gutschik, and E. Berbalk, *ibid.*, **91**, 794 (1960).

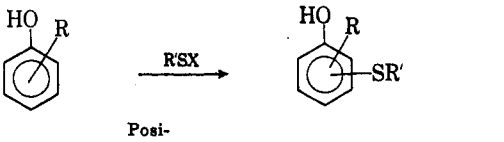
TABLE I




| RS | R' | R'' | Catalyst, mole fraction | Time, hr. | B.p., °C. (mm.) | Yield, % | | Analysis, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|
| 2-$CH_3S$[a] | H | H | 5.0 $H_3PO_4$ | 16 | 115–117 (14) | 6[b] | 16[c] | 22.9 | 22.8 |
| 4-$CH_3S$[d] | H | H | | | 146–148 (10) | 28 | 76 | 22.9 | 22.9 |
| | | | 0.20 $CH_3SO_3H$ | 2 | | 17 | 32 | | |
| | | | .02 $H_2SO_4$ | 5 | | 21 | 64 | | |
| | | | .25 $H_2SO_4$ | 5 | | 34 | 76 | | |
| | | | .50 $H_2SO_4$ | 5 | | 46 | 80 | | |
| | | | 1.00 $H_2SO_4$ | 5 | | 37 | 42 | | |
| 4-$CH_3S$[e] | 2-$CH_3$ | H | 5.0 $H_3PO_4$ | 16 | 108–109 (1) | 21 | 72 | 20.8 | 20.9 |
| | | | 0.10 $C_6H_5SO_3H$ | 1.5 | | 14 | 46 | | |
| 4-$CH_3S$ | 3-$CH_3O$ | H | .10 $H_2SO_4$ | 5 | 154–156 (4) | 20 | 61 | 18.8 | 19.0 |
| 2-$CH_3S$[f] | 4-$CH_3$ | H | .02 $H_2SO_4$ | 5 | 145–148 (10) | 4 | .. | 20.8 | 21.0 |
| 2-$CH_3S$[g] | 4-Cl | H | .02 $H_2SO_4$ | 5 | 126–128 (2) | 5 | 71 | 18.3 | 18.5 |
| 4-$CH_3S$ | 2-$C(CH_3)_2$ | H | .50 $H_2SO_4$ | 5 | 140–142 (4) | 13 | .. | 16.3 | 15.4 |
| 4-$CH_3S$ | 2-$C_6H_5$ | H | .05 $H_2SO_4$ | 5 | 198–200 (16) | 12 | 77 | 14.8 | 14.7 |
| 4-$CH_3S$ | 3-$CH(CH_3)_2$ | H | .05 $H_2SO_4$ | 5 | 145–147 (6) | 28 | 97 | 17.6 | 17.4 |
| 4-$CH_3S$ | 3-$C_2H_5$ | H | .05 $H_2SO_4$ | 5 | 135–137 (4) | 23 | 90 | 19.0 | 18.6 |
| 4-$CH_3S$ | 2-$CH(CH_3)_2$ | 5-$CH_3$ | .10 $H_2SO_4$ | 5 | 130–132 (2) | 28 | 96 | 16.3 | 16.2 |
| 4-$CH_3S$ | 2-$CH_3$ | 5-$CH(CH_3)_2$ | .06 $H_2SO_4$ | 5 | 157–158 (10) | 16 | 78 | 16.3 | 15.9 |
| 4-$CH_3S$ | 3-$CH_3$ | 5-$CH_3$ | .02 $H_2SO_4$ | 5 | 155–157 (16) | 15 | 68 | 19.0 | 19.3 |
| 4-$CH_3S$ | 3-$CH(CH_3)_2$ | 5-$CH(CH_3)_2$ | .05 $H_2SO_4$ | 5 | 154–156 (12) | 26 | 86 | 14.3 | 14.2 |
| 4-$CH_3S$ | 2-$CH(CH_3)_2$ | 6-$CH(CH_3)_2$ | .50 $H_2SO_4$ | 3 | 164–165 (12) | 48 | 63 | 14.3 | 14.2 |
| 2-$C_2H_5S$[h] | H | H | .02 $H_2SO_4$ | 3 | 115–118 (12) | 6 | 18 | 20.9 | 21.0 |
| 4-$C_2H_5S$[d] | H | H | | | 150–151 (12) | 22 | 65 | 20.9 | 21.4 |
| 4-$C_2H_5S$ | 3-$CH_3$ | H | .10 $H_2SO_4$ | 3 | 159–161 (12) | 8 | 42 | 18.9 | 18.6 |
| 4-$C_2H_5S$ | 3-$CH_3O$ | H | .02 $H_2SO_4$ | 7 | 163–166 (5) | 11 | 72 | 17.4 | 17.6 |
| 4-$C_2H_5S$ | 2-$CH(CH_3)_2$ | 5-$CH_3$ | .05 $H_2SO_4$ | 12 | 170–173 (15) | 25 | 85 | 15.6 | 15.5 |
| 4-$CH_3(CH_2)_3S$[d] | H | H | .20 $H_2SO_4$ | 3 | 164–165 (5) | 36 | .. | 17.6 | 17.3 |
| 4-$(CH_3)_2CHCH_2S$[d] | H | H | .18 $H_2SO_4$ | 8 | 152–154 (5) | 34 | .. | 17.6 | 16.8 |
| 4-$CH_3(CH_2)_4S$[d] | H | H | .20 $H_2SO_4$ | 7 | 188–190 (15) | 32 | .. | 16.3 | 15.8 |

[a] H. S. Holt and E. E. Reid, *J. Am. Chem. Soc.*, **46**, 2334 (1924). [b] Yield based on disulfide. [c] Yield based on phenol reacted. [d] E. Miller and R. R. Read, *J. Am. Chem. Soc.*, **55**, 1224 (1933). [e] S. Oae and C. C. Price, *ibid.*, **80**, 3425 (1958). [f] See ref. 5. [g] K. Brand and W. Groebe, *J. prakt. Chem.*, **108**, 1 (1924). [h] W. E. Parham and G. L. Willette, *J. Org. Chem.*, **25**, 53 (1960).

TABLE II




| R | R'SX | Position R | Position S | M.p., or b.p., °C. (mm.) | % Yield | Analysis, % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| H | $CH_3SCl$[a] | 2 | | | 6 | .. | .. |
| | | 4 | | | 38 | .. | .. |
| H | $CH_3SBr$ | 4 | | | 18 | .. | .. |
| 2-$CH_3$ | $CH_3SCl$ | 4[b] | | 105–107 (2) | 21 | 20.8 | 21.1 |
| 3-$CH_3$ | $CH_3SCl$ | 4 | | 108–109 (2) | 73 | .. | .. |
| 2-Cl | $CH_3SCl$ | 4[c] | | 135–136 (2) | 18 | 18.3 | 18.3 |
| 4-Cl | $CH_3SCl$ | 2 | | | 6 | .. | .. |
| 4-Br | $CH_3SCl$ | 2 | | 55 | 4 | 14.7 | 14.4 |
| 3-$CH_3O$ | $CH_3SCl$ | 4 | | | 32 | .. | .. |
| 2-$CH(CH_3)_2$ | $CH_3SCl$ | 4 | | 149–150 (6) | 37 | 17.6 | 17.2 |
| H | $C_2H_5SCl$[d] | 4 | | | 37 | .. | .. |
| 2-$CH(CH_3)_2$ | $n$-$C_5H_{11}SCl$[e] | 4 | | 185–191 (10) | 12 | 13.6 | 12.8 |
| H | $n$-$C_4H_9SCl$[e] | 4 | | | 16 | .. | .. |

[a] H. Brintzinger and K. M. Langheck, *Ber.*, **83**, 87 (1950). [b] D. Delfs and K. Wedemeyer, U. S. Patent 2,995,608 (1961). [c] S.-L. Chien and L.-Y. Yin, *J. Chinese Chem. Soc.* (Taiwan), **7**, 40 (1939) [*Chem. Abstr.*, **34**, 1980 (1940)]. [d] I. B. Douglass, K. R. Brower, and F. T. Martin, *J. Am. Chem. Soc.*, **74**, 5770 (1952). [e] H. Brintzinger and K. M. Langheck, *Ber.*, **87**, 325 (1954).

TABLE III

ALKALINE HYDROLYSIS OF HALO THIOANISOLES

| 4-$XC_6H_4SCH_3$ | Temp., °C. | Time, hr. | Yield, % |
|---|---|---|---|
| $BrC_6H_4SCH_3$[a] | 200–225 | 3.0 | 79 |
| $BrC_6H_4SCH_3$ | 250–275 | 1.5 | 61 |
| $BrC_6H_4SCH_3$ | 250–275 | 3.0 | 61 |
| $ClC_6H_4SCH_3$[b] | 200–225 | 3.0 | 9[c] |
| $ClC_6H_4SCH_3$ | 250–275 | 1.5 | 43[d] |
| $ClC_6H_4SCH_3$ | 250–275 | 3.0 | 57 |
| $ClC_6H_4SCH_3$ | 275–300 | 8.0 | 0 |

[a] M. P. Balfe, J. Kenyon, and E. E. Searle, *J. Chem. Soc.*, 380 (1951). [b] H. Gilman and N. J. Beaker, *J. Am. Chem. Soc.*, **47**, 1449 (1925). [c] 81% of $ClC_6H_4SCH_3$ recovered. [d] 45% of $ClC_6H_4SCH_3$ recovered.

ment with those reported in the literature. The infrared spectra of the alkylmercaptophenols contained a weak band near 700 cm.$^{-1}$ associated with the thioether linkage.[10]

## Experimental

**4-Methylmercapto-3-cresol (Phosphoric Acid Method).**—Seventy-five grams of phosphorus pentoxide and 400 g. of 85% phosphoric acid were heated with stirring in an open flask until a temperature of 180° was reached. One mole of *m*-cresol was

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 354.

added, the mixture was heated to 165°, and treated dropwise, over a 2-hr. period, with one mole of dimethyl disulfide at such a rate that the reaction temperature was maintained above 150°. The mixture was stirred at reflux for an additional 14 hr. and the organic layer was withdrawn, washed with a small amount of saturated sodium sulfate solution, and fractionated. There was obtained 33 g. (21%) of 4-methylmercapto-3-cresol, b.p. 108–109° (1 mm.); benzenesulfonate, m.p. 79–80°; phenyl carbamate, m.p. 106–107°.

**4-Methylmercaptophenol (Phosphoric Acid Method).**—A mixture of 45 g. of phosphorus pentoxide, 155 g. of 85% phosphoric acid, and 47 g. of phenol was treated over a 2-hr. period with 94 g. of dimethyl disulfide at such a rate that a temperature of 150–155° was maintained. Heating was continued for two additional hours after which the catalyst layer was withdrawn. The organic layer was washed with saturated sodium sulfate solution and fractionated to give 33 g. (47%) of 4-methylmercaptophenol, b.p. 146–148 (10 mm.). The recovered catalyst layer (after heating in an open flask to 180°), 47 g. of phenol, and 94 g. of dimethyl disulfide when treated as previously described in two consecutive experiments yielded 42 g. (60%) and 49 g. (70%) of 4-methylmercaptophenol, respectively.

**4-Methylmercaptophenol (Ion-Exchange Method).**—A mixture of 94 g. of phenol and 60 g. of resin AG50-X12 (Bio-Rad Laboratories) was treated dropwise, with stirring at 150°, with 75 g. of dimethyl disulfide during 4 hr. The reaction mixture was heated for two additional hours, cooled, and filtered. The resin was washed with five 100-ml. portions of chloroform, and the combined filtrates were fractionated to yield 43 g. (31%) of 4-methylmercaptophenol.

**4-Methylmercaptophenol (Sulfuric Acid Method).**—A mixture of one mole of phenol and 0.5 mole of concentrated sulfuric acid was heated rapidly to 170° and then cooled to 155°. One mole of dimethyl disulfide was added to the reaction mixture at such a rate that a reaction temperature of 150–155° was maintained. The reaction mixture was heated at 160–170° for an additional 2 hr. and treated as in the ion-exchange method. There was obtained 12 g. (8%) of 2-methylmercaptophenol, b.p. 115–117° (14 mm.), and 65 g. (46%) of 4-methylmercaptophenol, b.p. 146–148° (10 mm.); benzenesulfonate, m.p. 57–58°; phenyl carbamate, m.p. 145–146°.

**4-Methylmercapto-2,6-diisopropylphenol (Sulfenyl Chloride Method).**—A freshly prepared solution of 0.74 mole of methanesulfenyl chloride in 60 ml. of carbon tetrachloride was added during 30 min. to a solution of 0.37 mole of 2,6-diisopropylphenol in 60 ml. of dry carbon tetrachloride while the reaction temperature was maintained at −20° during the addition. The reaction mixture was then allowed to warm to room temperature. It was stirred overnight, washed with saturated sodium sulfate solution, and fractionated to give 32 g. (48%) of 4-methylmercapto-2,6-diisopropylphenol, b.p. 164–165 (12 mm.).

**4-Methylmercaptophenol (Hydrolysis of 4-Bromothioanisole).**—A mixture of 0.2 mole of 4-bromothioanisole, 200 ml. of 10% sodium hydroxide, 7.5 g. of copper oxide, and 2.5 g. of copper powder was heated in a rocking autoclave at 200–225° for 3 hr. A maximum pressure of 560 p.s.i. developed. The reaction mixture was allowed to cool and was extracted with 20 ml. of benzene to remove unchanged 4-bromothioanisole. Upon acidification of the alkaline solution, an oil separated, which was fractionated to yield 22 g. (79%) of 4-methylmercaptophenol.

# Bis(2-bromoalkyl)malononitriles by Addition of Dibromomalononitrile to Alkenes

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The addition of dibromomalononitrile to olefins is catalyzed by free-radical initiators and some metal halides. The structures of the products are consistent with a free radical mechanism.

Although dibromomalononitrile was reported over sixty years ago[1] little is known of its reactivity.[2,3] The discovery of its reaction with copper powder to yield tetracyanoethylene[4] has prompted study of its reactions with unsaturated compounds. Reaction with cyclohexene in the presence of copper powder was found[4] to yield cyclohexylidenemalononitrile, believed to result from initial formation of 7,7-dicyanobicyclo-[4.1.0]heptane followed by thermal rearrangement. It was suggested that this reaction and the formation of tetracyanoethylene may have proceeded through intermediate formation of dicyanocarbene.[4]

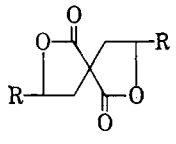
It has now been found that dibromomalononitrile reacts with terminal olefins to yield primarily 1:2 adducts.[5] Thus, dibromomalononitrile adds to ethylene

$$Br_2C(CN)_2 + 2C_2H_4 \xrightarrow{150^\circ} Br-CH_2-CH_2-\underset{\displaystyle CN}{\overset{\displaystyle CN}{\overset{|}{\underset{|}{C}}}}-CH_2-CH_2-Br$$

I

at 150° under a pressure of 1000 atm. to give 1,5-dibromo-3,3-dicyanopentane (I) in 71% yield.

The structure is assigned on the basis of the $A_2B_2$ pattern of the n.m.r. spectrum. Chemical confirmation of the structure was provided by conversion of I to the known spirolactone IIa.[6]



IIa, R = H
IIb, R = $n$-$C_4H_9$

1-Hexene, styrene, and 3-methylenecyclobutanecarbonitrile reacted with dibromomalononitrile at 60–80° to give 1:2 adducts. The reaction product of 1-hexene with dibromomalononitrile is more complex than that with ethylene in giving two isomeric products whose structures could differ in the mode of addition to 1-hexene (III, IV, or V) or in the diastereomeric forms of the adducts.

The structural question was conveniently resolved by n.m.r. spectroscopy which showed III to be the structure of both isomers. It seems most likely that the products isolated are the *meso* and *d,l* forms of III.

(1) B. C. Hesse, *Am. Chem. J.*, **18**, 723 (1896).
(2) L. Ramberg and S. Wideqvist, *Arkiv. Kemi, Mineral Geol.*, **12A**, No. 22, 12 pp. (1937).
(3) E. Ott and H. Finken, *Ber.*, **58B**, 1703 (1925).
(4) T. L. Cairns, *et al.*, *J. Am. Chem. Soc.*, **80**, 2775 (1958).
(5) K. Torssell and K. Dahlqvist, *Acta Chem. Scand.*, **16**, 346 (1962), published their work during the preparation of our paper. Our latest experiments with excess dibromomalononitrile agreed with their results in giving 1:1 adducts.
(6) H. Leuchs and E. Gieseler, *Ber.*, **45**, 2121 (1912).