The Activation of Bivalent Sulfur Compounds with Cupric Chloride and Zinc Chloride. The Benzylation and Acylation of Aromatic Compounds with Sulfides and Thiol Esters

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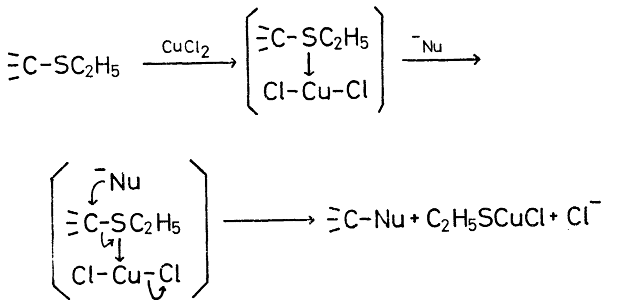
(Received April 4, 1973)

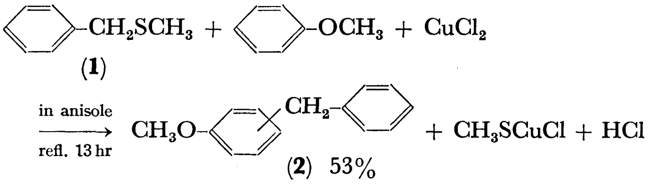
Benzylation of aromatic compounds, such as anisole, *m*-xylene, toluene, and benzene, with various benzyl sulfides in the presence of equimolar amounts of cupric chloride and zinc chloride was investigated. For example, in the case of benzylation of anisole with 4-benzylthiopyridine, *o*- and *p*-benzylanisoles were obtained in 79% yield in the presence of cupric chloride and zinc chloride. On the other hand, when the reaction was carried out in the presence of cupric chloride alone, the yield of benzylanisoles was low. The similar activation with cupric chloride and zinc chloride was successfully applied to the reaction of aromatic compounds with benzaldehyde diethylthioacetal and to the acylation of aromatic compounds with 1,2-bis(acylthio)ethanes.

The benzylation of aromatic compounds such as anisole, *m*-xylene, toluene, and benzene with benzyl sulfides in the presence of cupric chloride and zinc chloride were reported briefly in the previous paper.[1] In this report, these reactions are explained in detail with additional new results.

During the investigation on carbon–carbon bond forming reactions using benzaldehyde diethylthioacetal, benzophenone diethylthioacetal, and ethyl orthotrithioformate, it was found that these compounds react readily with active methylene compounds or anisole in the presence of cupric chloride to give the condensation or substitution products.[2] The reaction would be reasonably explained by considering an initial formation of a reactive intermediate, a coordinated compound of the bivalent sulfur compound with cupric chloride, which in turn is attacked by nucleophiles to give condensation or substitution products.



Based on the result, the reaction of sulfides with aromatic compounds was further investigated with the expectation that the sulfides would also be activated by the coordination with cupric chloride. When an anisole solution of equimolar amounts of benzyl methyl sulfide (**1**) and cupric chloride was heated to reflux, the generation of hydrogen chloride was observed immediately. After being stirred for 13 hr under reflux, the resulting precipitates were filtered off and the filtrate was concentrated under reduced pressure. Through the purification by silica gel column chromatography and distillation, *o*- and *p*-benzylanisoles (**2**, bp 115—116 °C/1.5 mmHg) were obtained in 53% yield.



(**1**) (**2**) 53%

In order to increase the yield of benzylated products, a variety of benzyl sulfides (**3**), in which RS group would be stabilized by the resonance effect as an anion, was used in place of **1** in the above reaction. However, the yields of **2** were poor by the treatment of **3** in refluxing anisole in the presence of an equimolar amount of cupric chloride for 5 hr as shown in Table 1.

This result suggests that, only by the examination into the structure of leaving group (RS–), benzyl sulfides (**3**) are not sufficiently activated for generation of benzyl cation. Then, the coupled use of cupric chloride and zinc chloride was examined according to the assumption that the electron density of benzylic carbon would be decreased by coordination of zinc chloride to ring nitrogen atom. In fact, when the anisole solution of 4-benzylthiopyridine (**3e**) and equimolar amounts of cupric chloride and zinc chloride was heated to reflux for 5 hr, the yield of **2** was increased up to 79%. Similarly, in the reaction of other sulfides, yields of **2** were remarkably increased by the combined use of cupric chloride and zinc chloride. The results are shown in Table 1.

The yields of **2** were hardly improved and **2** were obtained in less than 10% yield when the some typical Lewis acids such as aluminum chloride, stannic chloride, ferric chloride, and boron trifluoride diethyletherate were used together with cupric chloride in place of zinc chloride. Among various Lewis acids examined, it was apparently shown that zinc chloride is most effective when it was used together with cupric chloride, but **2** could not be detected when zinc chloride was used alone. Then in order to examine the possibility that the increase of the yield may result from a coordination of zinc chloride to ring nitrogen atom of sulfides, the reaction of benzyl methyl sulfide (**1**) having no nitrogen atom in a molecule was investigated in the presence of equimolar amounts of cupric chloride

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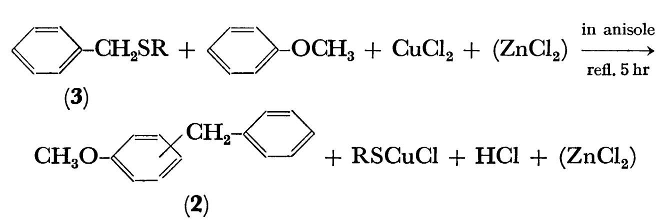
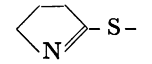
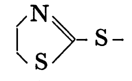
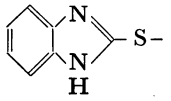
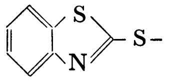
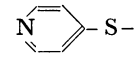
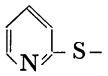
[1] T. Mukaiyama, K. Maekawa, and K. Narasaka, *Tetrahedron Lett.*, **1970**, 4669.

[2] T. Mukaiyama, K. Narasaka, and H. Hokonoki, *J. Amer. Chem. Soc.*, **91**, 4315 (1969); T. Mukaiyama, K. Narasaka, K. Maekawa, and H. Hokonoki, This Bulletin, **43**, 2549 (1970).

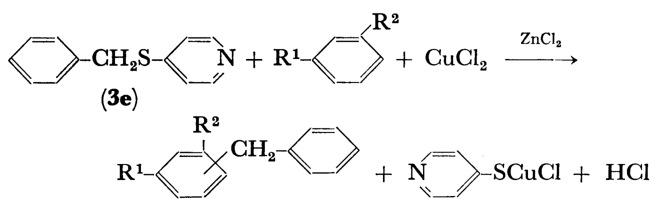
Table 1.



3 RS-	Yield of **2** (%) CuCl$_2$	CuCl$_2$+ZnCl$_2$
a) 	17	34
b) 	18	57
c) 	28	61
d) 	6	66
e) 	2	79
f) 	34	79

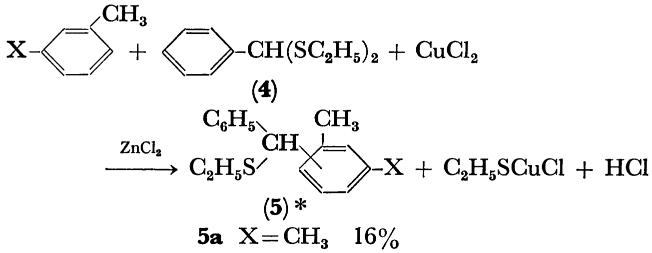
and zinc chloride. When anisole solution of **1**, cupric chloride and zinc chloride was heated to reflux for 5 hr, the yield of **2** was increased up to 76% as compared with the previous reaction using cupric chloride alone. The result indicates that zinc chloride would activate cupric chloride or the complex of cupric chloride with sulfide rather form a coordinated compound with sulfide.

In a similar way, the benzylation of other aromatic compounds such as *m*-xylene, toluene, and benzene with 4-(benzylthio)pyridine (**3e**) was carried out by the combined use of cupric chloride and zinc chloride, and the corresponding benzylated products, benzylxylenes, *o*- and *p*-benzyltoluenes, and diphenylmethane were obtained in 54, 34, and 15% yields respectively.



R^1	R^2	Yield (%)
CH$_3$	CH$_3$	54
CH$_3$	H	34
H	H	15

Previously, it was shown that benzaldehyde diethylthioacetal (**4**) reacts with anisole in the presence of cupric chloride to give the substituted product in good yield. On the other hand, it was shown that **4** did not react with other aromatic compounds such as *m*-xylene and toluene. The present method for the activation of sulfides with cupric chloride and zinc chloride was successfully applied to the reaction of **4** with *m*-xylene or toluene. When **4** was treated with *m*-xylene or toluene in the presence of equimolar amounts of cupric chloride and zinc chloride for 5 hr at room temperature, phenylxylylmethyl ethyl sulfides (**5a**) or phenyltolylmethyl ethyl sulfides (**5b**) were obtained in 16 or 11% yield.

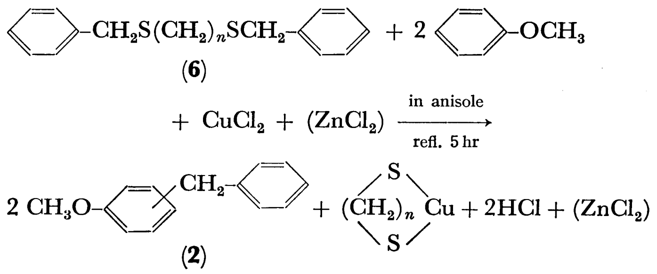


5a X=CH$_3$ 16%
5b X=H 11%

* These structures are supported by elemental analysis and mass spectrum, but the study of structural isomerism remains not to be examined.

α,ω-Bis(benzylthio)alkanes (**6**) were also used effectively for the benzylation of aromatic compounds in place of the sulfides (**1** and **3**). It is expected that these sulfides (**6**) would form the chelate complexes by the intramolecular coordination of cupric chloride to the two sulfur atoms of the sulfide and benzyl cation would be easily generated. When **6** were treated in the presence of cupric chloride alone or cupric chloride and zinc chloride in refluxing anisole for 5 hr, benzylanisoles (**2**) were obtained as shown in Table 2.

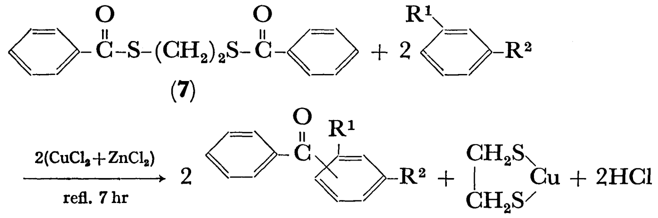
Table 2.



	n	Yield of **2** (%) CuCl$_2$	CuCl$_2$+ZnCl$_2$	2(CuCl$_2$+ZnCl$_2$)
6a	2	14	47	49
6b	3	11	56	58
6c	4	26	62	53

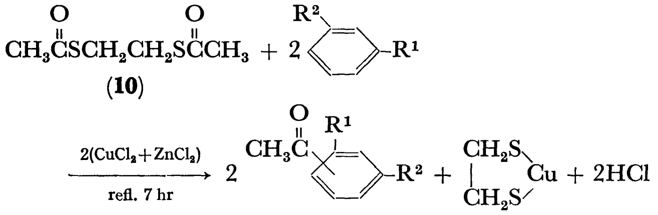
Bromobenzene was also benzylated by the reaction with 1,2-bis(benzylthio)ethane (**6a**) in the presence of equimolar amounts of cupric chloride and zinc chloride, and *o*- and *p*-bromophenylphenylmethanes were obtained in 14% yield.

Next, in order to examine the possibility of the cleavage of carbon–sulfur bond of thiolester by the use of cupric chloride and zinc chloride, the reaction of bis(acylthio)ethane with aromatic compounds was investigated. When anisole or *m*-xylene solution of 1,2-bis(benzoylthio)ethane (**7**) was heated to reflux in the presence of 2 equiv. of cupric chloride and zinc chloride for 7 hr, methoxybenzophenone (**8**) or phenylxylylketones (**9**) were obtained in 16 or 35% yield respectively together with about 15% of the recovered starting material (**7**).



(**8**) $R^1 = CH_3O-$, $R^2 = H$ 16%
(**9**) $R^1 = CH_3$, $R^2 = CH_3$ 35%

In a similar manner, 1,2-bis(acetylthio)ethane (**10**) reacted with anisole, *m*-xylene, and toluene to give acetylation products (**11, 12, 13**) together with unidentified products.



(**11**) $R^1 = CH_3O$, $R^2 = H$ 11%
(**12**) $R^1 = R^2 = CH_3$ 15%
(**13**) $R^1 = CH_3$, $R^2 = H$ 7%

In conclusion, it is noted that sulfides are sufficiently activated by the combined use of cupric chloride and zinc chloride and are attacked by aromatic compounds such as anisole, *m*-xylene, and toluene along with the cleavage of carbon–sulfur bond to form substitution products. This method for activation of sulfides by cupric chloride was successfully applied to our works of hydrolysis of 1,3-dithianes and reductive desulfurization of sulfides.[3]

Experimental

Materials. Commercially available cupric chloride and zinc chloride were used. They were dried over phosphorus pentoxide *in vacuo* at about 130 °C before use.

Benzyl methyl sulfide (**1**) and benzaldehyde diethylthioacetal (**4**) were prepared according to the procedures in literatures and purified by distillation: **1**, bp 97—101 °C/27 mmHg;[5] **4**, 135—136 °C/8 mmHg.[6]

Benzyl sulfides (**3a**—**f**) and α,ω-bis(benzylthio)alkanes (**6a**—**c**) were prepared by the treatment of the corresponding thiols with benzyl chloride in 95% ethanol in the presence of sodium hydroxide: **3a**, bp 120 °C/2 mmHg (lit, bp 134—135 °C/4 mmHg);[7] **3b**, bp 145—147 °C/1 mmHg (lit, bp 159—163 °C/3 mmHg);[8] **3c**, mp 184—185 °C (lit, mp 182—183 °C);[9] **3d**, mp 39—40 °C (lit, mp 40—41 °C);[10] **3e**, mp 64—65 °C (lit, mp 61—62 °C);[11] **3f**, bp 145—146 °C/2 mmHg (lit, bp 92—94 °C/0.1 mmHg);[11] **6a**, mp 34—35 °C (lit, mp 38 °C);[12] **6b**, bp 158 °C/0.07 mmHg (lit, bp 218—221 °C/8—9 mmHg);[13] **6c**, bp 167 °C/0.08 mmHg (Found: C, 71.38; H, 7.11; S, 21.30%. Calcd for $C_{18}H_{22}S_2$: C, 71.50; H, 7.11; S, 21.17%).

Thiolesters (**7**) and (**10**) were prepared by treatment of the petroleum ether solution of 1,2-ethanedithiol and pyridine with the corresponding acyl chlorides at 0 °C: **7**, mp 95 °C (lit, mp 96 °C);[14] **10**, mp 68—69 °C (lit, mp 68—73 °C).[15]

*Reaction of Benzyl Methyl Sulfide (**1**) with Anisole in the Presence of an Equimolar Amount of Cupric Chloride.* A mixture of **1** (1.38 g, 0.01 mol), cupric chloride (1.35 g, 0.01 mol) and dry anisole (30 ml) was heated to reflux for 13 hr. The color of the solution turned black and white precipitates formed. The precipitates were filtered off and the filtrate was concentrated under reduced pressure. The residue was then purified by silica gel column chromatography. The eluate with petroleum ether was concentrated and distilled, giving 1.05 g (53%) of benzylanisoles (**2**) (bp 115—116 °C/1.5 mmHg). The isomer ratio (*para* to *ortho*) of benzylanisoles was determined to be about 2 by two sets of singlets at τ 6.50 and 6.47 (ratio 2: 1, total area 3H) due to the methyl group. Found: C, 84.63; H, 7.07%. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12%. IR: 2830(OCH_3), 1030(C–O) cm^{-1}. Mass: M^+ 198, *m/e* 183[M^+–CH_3], *m/e* 167[M^+–OCH_3], *m/e* 121[M^+–C_6H_5], *m/e* 91[$C_6H_5CH_2^+$]. NMR: (in CCl_4) τ 6.50 (s, 2H, *p*-OCH_3), 6.47 (s, 1H, *o*-OCH_3), 6.25 (s, 1.3H, *p*-$C_6H_5CH_2$), 6.12 (s, 0.7H, *o*-$C_6H_5CH_2$–), 2.40—3.45 (m, 9H, aromatic protons).

Benzyl sulfides (**3a**—**f**) were treated in refluxing anisole with an equimolar amount of cupric chloride for 5 hr, and **2** was obtained according to the same procedure. The yields of **2** were listed in Table 1.

Reaction of 4-(Benzylthio)pyridine (3e) with Anisole in the Presence of Equimolar Amounts of Cupric Chloride and Zinc Chloride. A mixture of **3e** (2.01 g, 0.01 mol), cupric chloride (1.35 g, 0.01 mol), zinc chloride (1.36 g, 0.01 mol), and dry anisole (50 ml) was heated to reflux for 5 hr. According to the same procedure, benzylanisoles (**2**) were obtained (1.57 g, 79%).

Similarly, **3a**—**d** and **3f** were treated with equimolar amounts of cupric chloride and zinc chloride in refluxing anisole for 5 hr, and the yields of **2** were listed in Table 1.

Reaction of 4-(Benzylthio)pyridine (3e) with m*-Xylene in the Presence of Equimolar Amounts of Cupric Chloride and Zinc Chloride.* A mixture of **3e** (2.01 g, 0.01 mol), cupric chloride (1.35 g, 0.01 mol), zinc chloride (1.36 g, 0.01 mol) and dry *m*-xylene (50 ml) was heated to reflux for 7 hr. The reaction mixture was purified according to the same procedure as mentioned in the reaction of **1** with anisole, and phenylxylylmethanes (bp 115 °C/3 mmHg, 2 or 5- and 4-isomers in a ratio of 2: 13) were obtained in 54% (1.06 g) yield. Found: C, 92.03; H, 8.08%. Calcd for $C_{15}H_{16}$: C, 91.78; H, 8.22%. NMR: (in CCl_4) τ 7.92 and 7.80 (s, 5.2H, 4-isomer-CH_3), 7.85 (s, 0.8H, 2 or 5-isomer-CH_3), 6.20 (s, 1.7H, 4-isomer-$CH_2C_6H_5$), 6.08 (s, 0.3H, 2 or 5-isomer-$CH_2C_6H_5$).

Phenyltolylmethanes and diphenylmethane were also obtained by treating **3e** with toluene and benzene. Their

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[12] E. Fromm, H. Benzinger, and F. Scharfer, *Ann.*, **394**, 27 (1912).

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[14] S. Gabriel and P. Heymann, *ibid.*, **24**, 784 (1891).

[15] E. K. Ellingboe, U. S., 2423641, *Chem. Abstr.*, **42**, 3774¹ (1948).

physical properties and analytical data are as follows. Phenyltolylmethanes (*ortho* and *para* isomers in a ratio of 5: 4): bp 109—109.5 °C/3.5 mmHg. Found: C, 92.43; H, 7.90%. Calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74%. NMR: (in CCl_4) τ 7.85 (s, 1.3H, *p*-CH_3), 7.76 (s, 1.7H, *o*-CH_3), 6.18 (s, 1.1H, *o*-$CH_2C_6H_5$), 6.13 (s, 0.9H, *p*-$CH_2C_6H_5$). Diphenylmethane: bp 83 °C/4 mmHg. Found: C, 92.07; H, 7.30%. Calcd for $C_{13}H_{12}$: C, 92.81; H, 7.19%. Mass: M^+ 168, *m/e* 91 [$C_6H_5CH_2^+$].

Reaction of Benzaldehyde Diethylthioacetal (4) with m-*Xylene in the Presence of Equimolar Amounts of Cupric Chloride and Zinc Chloride.* A mixture of **4** (4.24 g, 0.02 mol), cupric chloride (2.69 g, 0.02 mol), zinc chloride (2.73 g, 0.02 mol), and dry *m*-xylene (50 ml) was stirred for 8 hr at room temperature and kept standing overnight. The precipitates were filtered off and the filtrate was concentrated under reduced pressure. The resulting oil was chromatographed on alumina gel. In order to hydrolyze the recovered **4**, the petroleum ether eluate was concentrated and treated in refluxing 95% ethanol in the presence of potassium hydroxide for half an hour. After removal of the solvent, the residue was extracted with ether and washed with water. The ether layer was concentrated and chromatographed on silica gel. The petroleum ether eluate was distilled and 0.98 g (16%) of phenylxylylmethyl ethyl sulfides (**5a**, bp 165 °C/4 mmHg) were obtained. Found: C, 79.40; H, 7.87; S, 12.57%. Calcd for $C_{17}H_{20}S$: C, 79.65; H, 7.86; S, 12.48%. Mass: *m/e* 195 [M^+–C_2H_5S], *m/e* 179 [M^+–C_6H_5], *m/e* 151 [M^+–$C_6H_3(CH_3)_2$]. Similarly, phenyltolylmethyl ethyl sulfides (**5b**, bp 150—151 °C/4 mmHg) were produced from **4** and toluene. Found: C, 79.52; H, 7.60; S, 12.78%. Calcd for $C_{16}H_{18}S$: C, 79.31; H, 7.49; S, 13.21%. Mass: *m/e* 181 [M^+–C_2H_5S], *m/e* 165 [M^+–C_6H_5], *m/e* 151 [M^+–C_6H_4-CH_3].

Reaction of 1,3-Bis(benzylthio)propane (6b) with Anisole in the Presence of Two Equimolar Amounts of Cupric Chloride and Zinc Chloride. A mixture of **6b** (2.88 g, 0.01 mol), cupric chloride (2.69 g, 0.02 mol), zinc chloride (2.73 g, 0.02 mol), and dry anisole (50 ml) was heated to reflux for 5 hr. The reaction mixture was treated according to the same procedure as in the case of the reaction of benzyl methyl sulfide (**1**) and anisole, and 2.22 g (56%) of benzylanisoles (bp 119—123 °C/3 mmHg) were obtained.

Reaction of 1,2-Bis(benzylthio)ethane (6a) with Bromobenzene in the Presence of Equimolar Amounts of Cupric Chloride and Zinc Chloride. A mixture of **6a** (2.74 g, 0.01 mol), cupric chloride (1.35 g, 0.01 mol), zinc chloride (1.36 g, 0.01 mol), and dry bromobenzene (50 ml) was heated to reflux for 6 hr. After filtration of a tarry substance, the filtrate was purified by silica gel column chromatography and distillation. Bromophenylphenylmethanes (*ortho* and *para* isomers in a ratio of 9: 11) were obtained, 0.69 g (14%) (bp 122 °C/1 mmHg). Found: C, 63.31; H, 4.60%. Calcd for $C_{13}H_{11}$-Br: C, 63.18; H, 4.49%. NMR: (in CCl_4) τ 6.34 (s, 1.1H, *p*-$C_6H_5CH_2$), 6.49 (s, 0.9H, *o*-$C_6H_5CH_2$), 2.40—3.30 (m, 9H). Mass: *m/e* 248 (M^++2) and 246 (M^+) (*ca.* 1: 1 ratio).

Reaction of 1,2-Bis(benzoylthio)ethane (7) with Anisole in the Presence of Equimolar Amounts of Cupric Chloride and Zinc Chloride. A mixture of **7** (6.04 g, 0.02 mol), cupric chloride (2.69 g, 0.02 mol), zinc chloride (2.73 g, 0.02 mol), and dry anisole (50 ml) was heated to reflux for 7 hr. The tarry substance sticked to the vessel was filtered off and the filtrate was chromatographed on silica gel. The petroleum ether eluate gave a viscous oil, which was fractionated by distillation to give 0.92 g of phenyl benzoate (bp 119—121 °C/4 mmHg, mp 70 °C) and 1.73 g of the starting material (**7**) (mp 93 °C). The benzene eluate was condensed and distilled to give 0.70 g (8%) of methoxybenzophenone (**8**, bp 156 °C/2.5 mmHg, mp 59—61 °C): Found: C, 79.03; H, 5.69%. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70%. IR: 2840 (OCH_3), 1638 (C=O), and 1020 (C–O) cm^{-1}. NMR: (in $CDCl_3$) τ 6.07 (s, 3H, OCH_3), 2.0—3.07 (m, 9H). The ether eluate gave 0.74 g of benzoic acid (mp 120—121 °C). The reaction of 1,2-bis(benzoylthio)ethane (**7**) with *m*-xylene was carried out according to the same procedure, and phenylxylylketones (**9**) were isolated in 35% yield, (bp 130 °C/1 mmHg, 2 or 5- and 4-isomers in a ratio of 1: 9). Found: C, 85.52; H, 6.71%. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71%. IR: 1665 (C=O) cm^{-1}. NMR: (in $CDCl_3$) τ 7.87 (s, 0.7H, 2 or 5-isomer-CH_3), 7.66 and 7.61 (s, 5.3H, 4-isomer-CH_3), 2.10—3.05 (m, 8H).

Reaction of 1,2-Bis(acetylthio)ethane (10) with Anisole in the Presence of Two Equimolar Amounts of Cupric Chloride and Zinc Chloride. A mixture of **10** (1.78 g, 0.02 mol), cupric chloride (2.69 g, 0.02 mol), zinc chloride (2.73 g, 0.02 mol), and dry anisole (50 ml) was heated to reflux for 7 hr. According to the same procedure as in the above experiment, 0.54 g of unidentified products and 0.32 g (11%) of methoxyacetophenone (**11**, bp 88 °C/1 mmHg) were obtained. Found: C, 71.42; H, 6.65%. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71%. NMR: (in $CDCl_3$) τ 7.48 (s, 3H, CH_3-CO), 6.16 (s, 3H, OCH_3), 2.0—3.15 (m, 4H). Mass: M^+ 150, *m/e* 135 [M^+–CH_3], *m/e* 107 [M^+–$COCH_3$].

Similarly, the reaction of **10** with *m*-xylene or toluene was carried out, and the physical properties and analytical data of the products (**12** or **13**) were as follwos. **12**: bp 103—104 °C/13 mmHg. Found: C, 80.43; H, 8.39%. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16%. NMR: (in CCl_4) τ 7.67 (s, 3H, CH_3), 7.52 (s, 6H, CH_3+$COCH_3$), 2.38—3.03 (m, 3H). Mass: M^+ 148, *m/e* 133 [M^+–CH_3], *m/e* 105 [M^+–$COCH_3$]. **13**: bp 84 °C/10 mmHg. NMR: (in CCl_4) τ 7.63 (s, 3H, $COCH_3$ or CH_3), 7.56 (s, 3H, CH_3 or $COCH_3$), 2.15—2.91 (m, 4H). Mass: M^+ 134, *m/e* 119 [M^+–CH_3], *m/e* 91 [M^+–$COCH_3$].