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The Condensation Reactions of Bivalent Sulfur Compounds-Copper(II) Complexes with Nucleophiles

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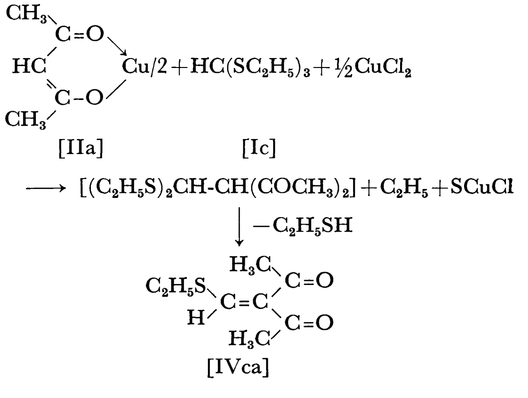
It was found that the bivalent sulfur compounds such as benzaldehyde diethylmercaptal, benzophenone diethylmercaptole, ethyl orthotrithioformate and benzyl methylsulfide, react with copper(II) salts of 1,3-dicarbonyl compounds, active methylene compounds or anisole, in the presence of cupric chloride, to give condensation or substitution products in good yields accompanied with carbon-sulfur bond cleavage. On the other hand, in the absence of cupric chloride, the bivalent sulfur compounds underwent no reaction and the starting materials were recovered. These results can be explained by assuming initial formation of active complexes from the bivalent sulfur compounds and copper(II).

The condensation reactions of bivalent sulfur compounds, such as benzaldehyde diethylmercaptal [Ia], benzophenone diethylmercaptole [Ib] and ethyl orthotrithioformate [Ic], with active methylene compounds were reported briefly in a previous paper[1]. In the present report, these reactions are explained in detail with new results.

The new condensation reaction of carbon-carbon bond formation accompanied with carbon-sulfur bond cleavage was carried out on the assumption that the bivalent sulfur compound would be activated by coordination with the so-called soft acids,[2] such as Cu(II), Ag(I) and Hg(II), forming a reactive complex. Copper(II) was chosen as the acid because it has a soft character and is known to form mercaptide easily. The coordinated compounds of bivalent sulfur compounds and copper(II) would act as an electrophile and cleavage of the carbon-sulfer bond would occur without difficulty. Based on this assumption, the condensation reactions of the bivalent sulfur compounds [I] with nucleophilic reagents, such as copper(II) salts of 1,3-dicarbonyl compounds [II], active methylene compounds and anisole, were studied in the presence of cupric chloride.

Little work has been done on a synthetic study with the used of copper(II) salts of 1,3-dicarbonyl compounds [II] since they are very stable toward electrophiles.[3] For example, it is known that alkyl halide does not react with the copper(II) salts [II]. Instead, the condensation reaction occurs when 1,3-dicarbonyl compound is used as an alkali metal salt. In this reaction, *O*-substituted compound is always accompanied with *C*-substituted compound. On the other hand, when copper(II) salt is used for alkali metal salt, it is expected that the copper(II) atom would protect the *O*-position by chelation. Therefore, *C*-substituted products would result exclusively by treating copper(II) salts with bivalent sulfur compounds [I] under a nearly neutral condition.

At first, bis(acetylacetonato)copper(II) [IIa] and ethyl orthotrithioformate [Ic] were refluxed in dioxane, but the reaction did not occur and the starting materials were recovered quantitatively. However, when a half molar amount of cupric chloride was added to the tetrahydrofuran [THF] solution of Ic and IIa, the blue precipitate of IIa disappeared and a green precipitate appeared immediately. After being stirred for 8 hr and kept standing overnight, the green precipitate disappeared and a grey substance deposited. After filtration of the substance and purification by silica gel column chromatography and distillation, the condensation product, 3-(α-ethylthioethyl-



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[1] T. Mukaiyama, K. Narasaka and H. Hokonoki, *J. Amer. Chem. Soc.*, **91**, 4315 (1969).

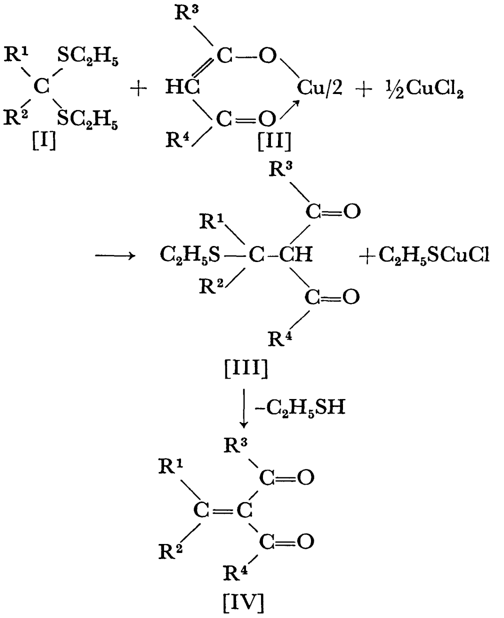
[2] R. G. Pearson and J. Songstad, *ibid.*, **85**, 3533 (1963); R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

[3] M. Conrad and M. Guthzert, *Ber.*, **19**, 19 (1886); H. D. Murdock and D. C. Nonhebel, *J. Amer. Chem. Soc.*, **84**, 2153 (1962).

idene)-pentane-2,4-dione [IVca] was obtained in 65% yield.

Similarly, bivalent sulfur compounds [Ia,b,c] reacted with copper(II) salts of 1,3-dicarbonyl compounds such as acetylacetone [IIa], dibenzoylmethane [IIb] or ethyl acetoacetate [IIc] in the presence of cupric chloride at room temperature and the condensation products, [III] or [IV], were obtained. The results are shown in Table 1.

TABLE 1

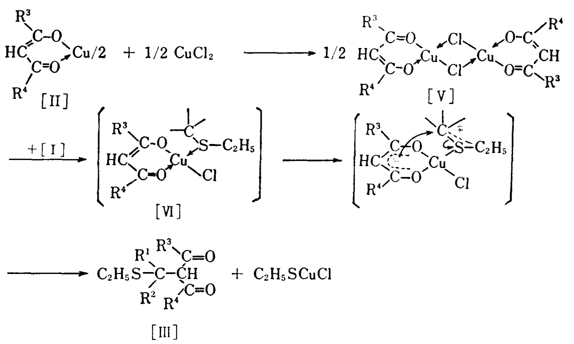


[I]		[II]		Yield,	%
R¹	R²	R³	R⁴	(III)	(IV)
H	C_2H_5S	CH_3	CH_3		65
H	C_6H_5	CH_3	CH_3	92	
C_6H_5	C_6H_5	CH_3	CH_3	55	
H	C_2H_5S	C_6H_5	C_6H_5	73	
H	C_6H_5	C_6H_5	C_6H_5	82	
H	C_2H_5S	CH_3	OC_2H_5	58	
H	C_6H_5	CH_3	OC_2H_5		46

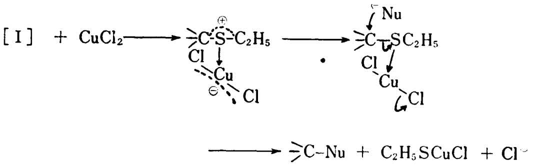
In all cases, *C*-substituted products were produced exclusively, as expected, and no detectable amount of *O*-substituted product was obtained.

In the absence of cupric chloride, the sulfur compounds [I] did not react with copper(II) salts [II] even at an elevated temperature, while, in the presence of cupric chloride the reaction proceeded smoothly under a mild condition.

This may be explained by assuming a double nuclear complex [V][4] of copper(II) salts [II] and cupric chloride. [V] readily affords chelate [VI] by coordination to a sulfur atom of bivalent sulfur compound [I]. Chelate [VI] thus formed decomposes into a condensation product [III] and ethylmercapto cupric chloride by way of an internal nucleophilic displacement as described in the following equation.



The result suggests that a complex of bivalent sulfur compounds [I] and cupric chloride would act as an electrophile and react with nucleophilic reagent [Nu⊖] giving a condensation product [>C–Nu] and ethylmercapto cupric chloride as shown below.



Based on this assumption, the reactions of sulfur compounds [I] and active methylene compounds in the presence of cupric chloride were investigated. Acetylacetone and benzaldehyde diethylmercaptal [Ia] were allowed to react for 12 hr at room temperature in the presence of 2 equimolar amounts of cupric chloride and an equimolar amounts of 2,6-lutidine, a hydrogen chloride catcher, in THF. After removal of the precipitate by filtration and purification by silica gel column chromatography, 3-(α-ethylthiobenzyl)pentane-2,4-dione was isolated in 79% yield as a white crystal. Similarly, 1,3-indandione, malononitrile or ethyl malonate reacted with sulfur compounds [Ia,b,c] to give condensation products, [VII] or [VIII]. The results are summarized in Table 2.

By this procedure, the condensation products can be directly prepared from 1,3-dicarbonyl compunds and sulfur compounds [I], without preparation of their copper(II) salts. It was confirmed that malononitrile and 1,3-indandione, which do not form their copper(II) salts, can react with sulfur compounds [I] in this way.

In the cases of cyclohexanone and benzaldehyde diethylmercaptal [Ia], a similar reaction did not occur and the starting materials were recovered. On the other hand, when they were refluxed in ether in the presence of 4 equimolar amounts of cupric chloride and a catalytic amount of $Et_2O\cdot$

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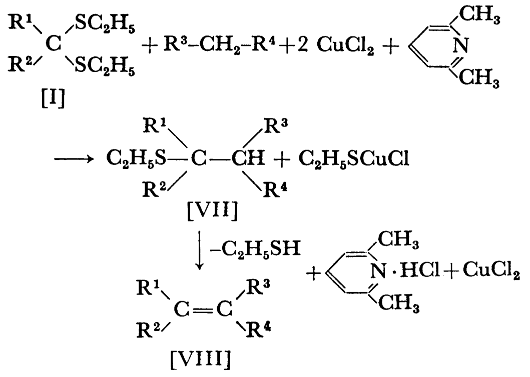
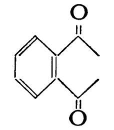
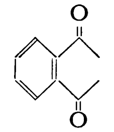
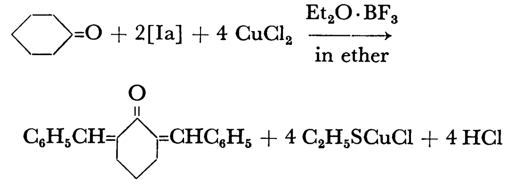
[4] The double nuclear complex of IIa and cupric chloride, μ-dichloro-bis(acetylacetonato)dicopper(II), was isolated as a green precipitate by treating equimolar amounts of IIa and cupric chloride in THF under a dry nitrogen atmosphere. Elemental analysis gives $(C_5H_7O_2CuCl)_n$. It was found that the complex is readily hydrolyzed to give IIa and cupric chloride.

Table 2



[I]		Active methylene		Yield, %	
R^1	R^2	R^3	R^4	(VII)	(VIII)
C_6H_5	H	CH_3CO	CH_3CO	79	
C_6H_5	H	CN	CN		62
C_6H_5	H	$COOC_2H_5$	$COOC_2H_5$	63	
C_6H_5	H				53
C_2H_5S	H	CN	CN		45
C_2H_5S	H				62
C_6H_5	C_6H_5	CN	CN		64

BF_3, the condensation product, 2,6-dibenzylidenecyclohexanone [IX], was obtained in 62% yield.

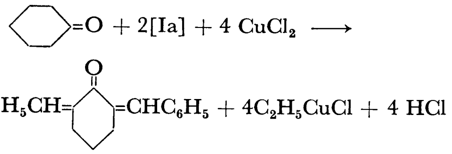


[IX]

The effects of the solvents on this type of reaction were studied by treating cyclohexanone and 2 equimolar amounts of Ia in the presence of 4 equimolar amounts of cupric chloride, in various solvents at room temperature. Among various solvents examined, ethyleneglycoldimethylether afforded the best result and the condensation product [IX] was obtained in 64% yield.

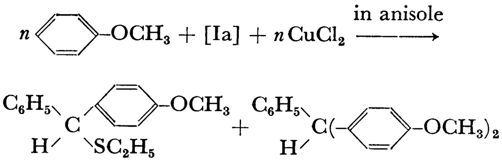
It was found that anisol also reacted with Ia,c and benzyl methylsulfide [XV] in the presence of cupric chloride to afford substituted products. When benzaldehyde diethylmercaptal [Ia] was treated in the presence of an equimolar amount of cupric chloride in anisole, even at room temperature, hydrogen chloride evolved vigorously and after purification by silica gel column chromatography, a monosubstituted compound, anisylphenylmethyl ethylsulfide [X] and a disubstituted product, dianisylphenylmethane [XI] were obtained in 62% and 19% yields, respectively. When the molar ratio of cupric chloride to Ia was increased to 2 or 3, the disubstituted compound [XI] only was formed in a good yield according to the following equation.

Table 3



[IX]

Solvent	[IX], Yield	Solvent	[IX], Yield
$C_2H_5OC_2H_5$	17%	CCl_4	45%
	15%	$CHCl_3$	28%
$(CH_3OCH_2)_2$	64%	CH_2Cl_2	41%
$(CH_3OCH_2CH_2)_2O$	50%	$(ClCH_2)_2$	35%
C_6H_{12}	24%	$CH_3COOC_2H_5$	53%
C_6H_6	58%	DMSO, DMF	0%

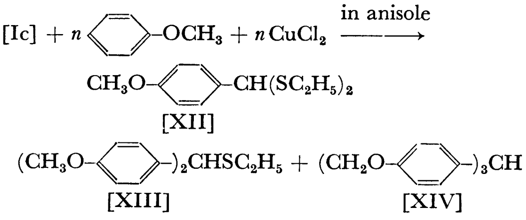


$+ nC_2H_5SCuCl + nHCl$

[X] [XI]

	Yield, %	
	[X]	[XI]
$n=1$	62	19
$n=2$		83
$n=3$		100

Similary, ethyl orthotrithioformate [Ic] reacted with anisole to give the following products.

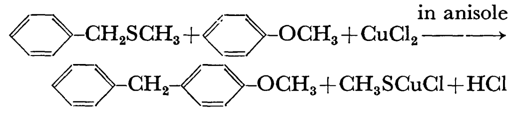


[XII] [XIII] [XIV]

$+ nCuCl_2 + nHCl$

	Yield, %		
	[XII]	[XIII]	[XIV]
$n=1$	5	31	
$n=2$			32
$n=3$			38

It was also confirmed that anisylphenylmethane [XVI], was obtained in 51% yield by refluxing benzyl methylsulfide [XV] in anisole in the presence of an equimolar amount of cupric chloride.



[XVI]

Experimental

Material. Commercial cupric chloride was used. It was ground and dried over phosphorus pentoxide *in vacuo* at about 130°C before use. Bivalent sulfur compounds, [Ia,b,c] and [XV] were prepared according to the procedures in literature and purified by distillation. [Ia][5] 135—136°C/8 mmHg; [Ib][5] 146—150°C/0.07 mmHg; [Ic][6] 129—132°C/14 mmHg; [XV][7] 97—101°C/27 mmHg.

Copper salts of 1,3-dicarbonyl compounds [IIa,b,c] were prepared from cupric acetate and 1,3-dicarbonyl compounds according to general procedure.[8]

Reaction of Bis(acetylacetonato)copper(II) [IIa] with Benzaldehyde Diethylmercaptal [Ia]. Into a suspension of 0.68 g (0.005 mol) of cupric chloride and 1.31 g (0.005 mol) of IIa in dry THF (35 m*l*) was added 2.12 g (0.001 mol) of Ia in one portion. The mixture was stirred for 8 hr and kept standing overnight at room temperature. After removal of 0.69 g of grey precipitate, the filtrate was concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (silica gel column chromatography was used in order to remove ethylmercapto cupric chloride completely.), and a white crystal, 3-(α-ethylthiobenzyl)-pentane-2,4-dione was obtained; 2.20 g (92%), mp 71—72°C (recrystallized from ethanol, mp 71.5—73°C). Found: C, 67.25; H, 7.33; S, 12.88%. Calcd for $C_{14}H_{18}O_2S$: C, 67.18; H, 7.25; S, 12.79%. The infrared spectrum showed a strong absorption band at 1690 cm^{-1} assigned to the C=O group. The NMR spectrum showed absorption bands at τ 8.86 (triplet) 3H, 8.68 (singlet) 3H, 7.68 (singlet) 3H, 7.22 (quartet) 2H, 5.83 (doublet) H, 5.51 (doublet) H and aromatic protons 5H.

Similarly, the condensation products [III] or [IV] were obtained by the reaction of copper(II) salts of 1,3-dicarbonyl compounds [IIa,b,c] with sulfur compounds [Ia,b,c]. Physical properties and analytical data are summarized in Table 4.

Isolation of μ-Dichloro-bis(acetylacetonato)dicopper(II) by the Reaction of Bis(acetylacetonato)-copper(II) [IIa] with Cupric Chloride. When 2.62 g (0.01 mol) of [IIa] and 1.36 g (0.01 mol) of cupric chloride were allowed to react in 200 m*l* of dry THF stirred in a dry nitrogen atmosphere, the blue precipitate of IIa disappeared immediately and a green precipitate appeared soon. The green substance was collected by filtration in a dry nitrogen atmosphere and washed with THF. It was then dried *in vacuo* and analyzed. Found: C, 32.32; H, 4.44; Cl, 17.37%. Calcd for $C_{10}H_{14}O_4Cu_2Cl_2$: C, 33.29; H, 3.91; Cl, 17.90%.

Reaction of Acetylacetone with Benzaldehyde Diethylmercaptal [Ia]. Into a suspension of 2.68 g (0.02 mol) of cupric chloride and 1.07 g (0.01 mol) of 2,6-lutidine in THF (35 m*l*), 1.00 g (0.01 mol) of acetylacetone and 2.12 g (0.01 mol) of Ia were added in one portion. The solution was then stirred for 12 hr and kept standing overnight at room temperature. After filtering off a solid (3.76 g,) the filtrate was evaporated under reduced pressure. Purification of the residue by silica gel column chromatography gave 1.96 g (79%) of 3-(α-ethylthiobenzyl)pentane-2,4-dione (mp 68—72°C), which showed an infrared spectrum identical with that of the authentic sample obtained by the above mentioned reaction.

TABLE 4

[I]		[II]		Products	Mp (Bp)	Anal Found (Calcd)		
R^1	R^2	R^3	R^4	[III]	[IV]	C	H	S
H	C_2H_5S	CH_3	CH_3		(121°C/1 mmHg)	55.76	6.81	18.80
						(55.80)	(7.03)	(18.59)
H	C_2H_5S	C_6H_5	C_6H_5	101—102°C		81.75	5.02	8.39
						(81.46)	(4.97)	(8.64)
H	C_2H_5S	CH_3	OC_2H_5		(129°C/1 mmHg)	53.62	7.21	15.86
						(53.46)	(6.98)	(15.82)
H	C_6H_5	CH_3	CH_3	71.5—73°C		67.25	7.33	12.88
						(67.18)	(7.25)	(12.59)
H	C_6H_5	C_6H_5	C_6H_5	111—113°C		76.75	5.97	8.47
						(76.98)	(5.92)	(8.55)
H	C_6H_5	CH_3	OC_2H_5		(115—115.5°C/3 mmHg)	64.57	7.46	10.78
						(64.27)	(7.19)	(11.42)
C_6H_5	C_6H_5	CH_3	CH_3	124.5—126°C		73.38	7.06	9.62
						(73.60)	(6.79)	(9.81)

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[5] M. L. Wolform and J. V. Karavinos, *J. Amer. Chem. Soc.*, **66**, 909 (1944).

[6] G. Holber, *Ber.*, **40**, 1740 (1907).

[7] J. V. Brown and P. Engelbertg, *ibid.*, **56**, 1573 (1923).

[8] H. D. Murdoch and D. C. Nonhebel, *J. Chem. Soc.*, **1962**, 2153.

TABLE 5

(I)	Active methylene	Products	Mp (Bp)	Anal, Found (calcd)			
		[VII]	[VIII]	C	H	N	S
Ia	Malononitrile		82.5—84°C	78.18	3.67	18.20	
				(77.90)	(3.92)	(18.17)	
Ia	Ethylmalonate	(137°C/0.6 mmHg)		62.09	6.89		10.21
				(61.92)	(7.15)		(10.31)
Ia	1,3-Indandione		152.—153°C	81.89	4.10		
				(82.04)	(4.30)		
Ib	Malononitrile		139.5—140.5°C	83.27	4.38	12.30	
				(83.45)	(4.38)	(12.17)	
Ic	Malononitrile		39—41°C	52.41	4.23	20.30	22.90
				(52.17)	(4.38)	(20.28)	(23.17)
Ic	1,3-Indandione		129—130.5°C	65.81	4.34		14.57
				(66.05)	(4.62)		(14.66)

Similarly, the products [VII] or [VIII] were obtained by treating acetylacetone, malononitrile, ethyl malonate and 1,3-indandione with Ia,b,c. Their physical properties and analytical data are shown in Table 5.

Reaction of Cyclohexanone with Benzaldehyde Diethylmercaptal [Ia] in the Presence of a Catalytic Amount of $Et_2O \cdot BF_3$. 4.24 g (0.02 mol) of [Ia], 0.98 g of cyclohexanone and three drops of $Et_2O \cdot BF_3$ were added to a suspension of 5.44 g (0.04 mol) of cupric chloride in 40 ml of ether. The mixture was refluxed for 2 hr with stirring and kept standing overnight at room temperature. 2,6-Dibenzylidenecyclohexanone [IX] was obtained through the same procedure as described in the above reaction. 1.72 g (62%) (recrystallized from ligroin; mp 115—117°C). Found: C, 87.64; H, 6.40%. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61%.

Reaction of Cyclohexanone with Benzaldehyde Diethylmercaptal [Ia] in Various Solvents. Into a suspension of 2.68 g (0.02 mol) of cupric chloride in 50 m*l* of solvent were added 0.49 g of cyclohexanone and 2.12 g (0.01 mol) of Ia. The mixture was then stirred for 7 hr and kept standing 15 hr at room temperature. The reaction mixture was purified in a similar manner as mentioned above. The yields of IX in various solvents are summarized in Table 3.

Reaction of Anisole with Benzaldehyde Diethylmercaptal [Ia]. A mixture of 6.36 g (0.03 mol) of Ia and 4.08 g (0.03 mol) of cupric chloride in dry anisole (50 m*l*) was stirred at room temperature. Hydrogen chloride was evolved vigorously. A white precipitate (1.07 g) was filtered off and the filtrate was condensed in reduced pressure. Two substances, an oily substance and a white crystal, were separated by silica gel column chromatography. The oily substance was then fractionated, giving 4.73 g (62%) of anisylphenylmethyl ethylsulfide [X]. bp 147—155°C/0.05 mmHg. Found: C, 74.11; H, 6.79; S, 12.13%. Calcd for $C_{16}H_{18}OS$: C, 74.39; H, 7.02 ;S, 12.38%. The white crystal was dianisylphenylmethane [XI]. 1.71 g (19%) (recrystallized from ethanol. mp 96—97°C). Found: C, 82.81; H, 6.35%. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62%. The NMR spectrum of both X and XI has only one absorption band assigned to OCH_3 group at τ 6.45 and 6.33, respectively. The results show that *para*-substituted products were obtained exclusively.

Reaction of Ethyl Orthotrithioformate [Ic] with Anisole in the Presence of an Equimolar Amount of Cupric Chloride. A mixture of 3.92 g (0.02 mol) of Ic and 2.72 g (0.02 mol) of cupric chloride in dry anisole (40 m*l*) was stirred for 12 hr and kept standing overnight at room temperature. Through the same procedure as described above, an oily substance was obtained and distilled *in vacuo*. Ic was recovered in 21% and 0.24 g (5%) of methoxybenzaldehyde [XII] (bp 162—164°C/0.08 mmHg) was obtained. In addition to XII, 1.78 g (31%) of dianisylmethylethylsulfide [XIII] was fractionated at 192°C/0.08 mmHg. Found: C, 71.11; H, 7.20; S, 11.10%. Calcd for $C_{17}H_{20}SO_2$: C, 70.81; H, 6.99; S, 11.17%.

Reaction of [Ic] with Anisole in the Presence of Two Equimolar Amounts of Cupric Chloride. When 5.44 g (0.04 mol) of cupric chloride was used in the above experiment, 2.13 g (32%) of trianisylmethane [XIV] was isolated. (recrystallized from ethanol. mp 56—58°C). Found: C, 78.72; H, 6.50%. Calcd for $C_{22}H_{22}O_3$: C, 79.01; H, 6.63%.

Reaction of Benzyl Methylsulfide [XV] with Anisole. When a mixture of 4.14 g (0.03 mol) of XV and 6.00 g (0.044 mol) of cupric chloride in 60 m*l* of dry anisole was refluxed for 11 hr, the color of the solution turned black and a white precipitate was deposited. The precipitate was filtered off and the filtrate was concentrated *in vacuo* and purified by silica gel column chromatography. The eluate was concentrated and distilled, giving 3.02 g (51%) of anisylphenylmethane [XVI] (bp 112—114°C/1.5 mmHg). Found: C, 85.03; H, 7.31%. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12%.