Organic Disulfides and Related Substances. 39. Study of Insertion Reactions Using Carbenoids, Carbenes, Ylides, and Nitrenes[1]

Lamar Field* and Catherine Hamrick Banks

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

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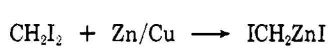
With the carbenoidal Simmons–Smith reagent (~ICH_2ZnI), several diaryl disulfides underwent insertion of CH_2 between the sulfur atoms to give bis(arylthio)methanes in yields up to 85% by NMR and 33% by isolation. Insertion of more than one CH_2 sometimes occurred. An alkyl and an aralkyl disulfide were recovered unchanged. This reaction proceeds reasonably well only with aryl disulfides lacking substituents that are ortho, strongly electron-withdrawing, or strongly basic in the Lewis sense. Carbenoids obtained from copper-catalyzed decomposition of diazo esters also gave insertion products. However, reactions were preferred that led to the same outcome through BF_3-catalyzed decomposition of the diazo esters; pure acids were isolated in 11–16% yield. Dichlorocarbene did not react with diaryl disulfides. With an ylide, triphenylphosphonium methylide, only trace insertion of CH_2 occurred with diphenyl disulfide. The major product was tris(phenylthio)methane (64% isolated); methyl phenyl sulfide, triphenylphosphine sulfide, and thiophenol also were isolated, and a course of reaction is suggested. Di-*n*-propyl disulfide evidently reacted similarly. Attempted insertion of R′N moieties by reaction of nitrenes with diphenyl disulfide was unpromising.

In a continuing study of organic disulfides,[1a] we became interested in the feasibility of insertions like that shown by eq 1.

$$\mathrm{RSSR} + \mathrm{Z} \longrightarrow \mathrm{RSZSR} \qquad (1)$$

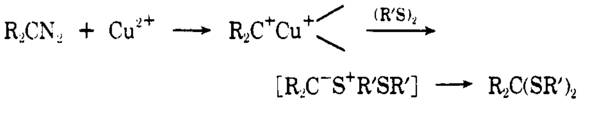
Carbenoids, carbenes, ylides, and nitrenes seemed promising species for insertions of a moiety Z. At the outset, the literature contained little information on such possibilities, although reports appeared later on carbenoids and, especially, carbenes.

Carbenoids. The Simmons–Smith reagent, formulated as 1 for simplicity, is a carbenoid readily available by the means of eq 2



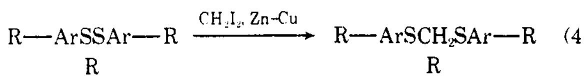
$$\mathrm{CH_2I_2} + \mathrm{Zn/Cu} \longrightarrow \underset{\mathbf{1}}{\mathrm{ICH_2ZnI}} \qquad (2)$$

among others.[2] Use of 1 in synthesis of cyclopropanes by insertion of CH_2 into carbon–carbon double bonds has been reviewed,[2] but reactions of 1 with disulfides have not been explored. The only study with disulfides of carbenoid reactions was of insertion into a cyclic disulfide by the use of substituted diazomethanes, with copper acetylacetonate as a catalyst (eq 3).[3] Diphenyl disulfide gave an unidentified product.[3]



(3)

As eq 4 shows, aryl disulfides **2–8** with the Simmons–Smith reagent underwent insertion of CH_2 to give the bis(arylthio)methanes **9–15**. Identities of **9–12** and **15** were assured by mixture melting point and congruity of NMR and ir spectra using authentic samples synthesized according to eq 5, a well-known method.[4]



$$\mathrm{R{-}\underset{R}{Ar}SSAr{-}R} \xrightarrow{\mathrm{CH_2I_2,\ Zn\text{-}Cu}} \mathrm{R{-}\underset{R}{Ar}SCH_2SAr{-}R} \qquad (4)$$

2, H	**6**, *p*-$(CH_3)_2N$	**9**, H	**13**, *p*-$(CH_3)_2N$
3, *p*-CH_3	**7**, *p*-H_2N	**10**, *p*-CH_3	**14**, *p*-H_2N
4, 2,3-$(CH_3)_2$	**8**, *p*-Cl	**11**, 2,3-$(CH_3)_2$	**15**, *p*-Cl
5, *p*-CH_3O		**12**, *p*-CH_3O	

$$\mathrm{2ArSNa} + \mathrm{CH_2I_2} \longrightarrow \mathrm{(ArS)_2CH_2} + \mathrm{2NaI} \qquad (5)$$

Yields of bis(arylthio)methanes were determined by NMR on the assumption that the reaction product contained only the disulfide used (e.g., **2–8**) and the bis(arylthio)methane (e.g., **9–15**); this assumption generally was reasonable, although **3** and **8** led to small amounts of other products discussed below. Validity of the NMR method was established with standard mixtures of **2** and **9**. Bis(arylthio)methanes **9–12** and **15** also were isolated in yields of 5–33% by column chromatography; with **9** and **10**, overlapping disulfide also required reduction ($LiAlH_4$) for purification entailing considerable loss, but with the 2,3-dimethyl, *p*-methoxy, and *p*-chloro compounds (**11**, **12**, **15**) pure products were obtained from the column.

We turn now to the individual reactions summarized by eq 4. Conversion of diphenyl disulfide (**2**) to bis(phenylthio)methane (**9**) afforded a good vantage point for studying characteristics of the general reaction, since it also would afford a good reference point for comparing effects of substitution. These studies gave the results a–f.

(a) When **2** was added near the end of the preparation of **1** in ether, variation of the ratio of **1**:**2** (from 1 to 2) and of time (20–72 hr) suggested that the best ratio was 1.5 and the best time about 20 hr.

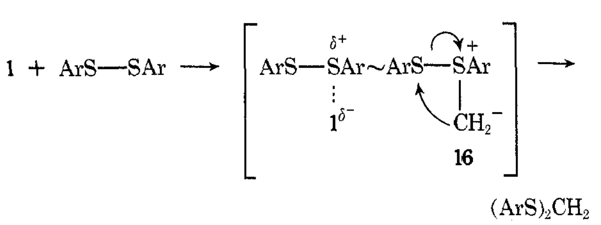
(b) When reagent **1** was prepared beforehand, so that the filtered, clear solution of **1** could be added to disulfide **2**, bis(phenylthio)methane (**9**) was obtained in a yield as high as 70% [but, for unknown reasons, also in yields as low as 2–7%; the tolyl analog (**10**) was obtained in 22% yield]. Although these yields suggest that this inverse addition is inferior to the usual mode, formation by this means is important because it proves that **9** and **10** arise in eq 4 from reagent **1**, not merely from reduction of the disulfide by zinc followed by alkylation of the zinc thiolate. This conclusion was buttressed among other ways (*vide infra*), by recovery of 77% of disulfide **2** (and of formation of only 1% of thiophenol) when **2** was subjected to the usual conditions of eq 4, except for omission of methylene iodide.

(c) Although a recent preparation of the reagent **1** often improves results,[5] its use led only to 98% recovery of **2**.

(d) Variations in the yield of **9** show that conditions are important. Presumably owing to uncertainties in the preparation of the zinc–copper couple[5] and to the heterogeneity of **1**, yields of **9** occasionally varied erratically from 85 to 10%, even under essentially the preferred conditions. In some experiments, iodine consumption showed that 10–22% of thiophenol also formed, reflecting some reduction of the disulfide. Recoveries of disulfide **2** in various reactions ranged from about 15 to 80%, but attempts to increase consumption of **2** by prolonging reaction beyond about 24 hr led only to tar, and larger ratios of **1** were not beneficial.

(e) In the isolation of **9**, several agents were tried in the hope of reducing contaminating disulfide to the thiol which could be removed with aqueous base. Glucose reduced bis(*p*-nitrophenyl) disulfide quantitatively but gave no help with **2** or other disulfides. Sodium borohydride led to incomplete reduction. Lithium aluminum hydride, as mentioned, partially destroyed **9**, but isolation of **9** in 25% yield (yield by NMR 85%) finally was achieved by using this hydride repeatedly, with chromatography.

(f) The most attractive rationalization of the reaction of eq 4 is that reagent **1** attacks the disulfide bond as an electrophile and that a ylide-like species produced then rearranges (eq 6).



(6)

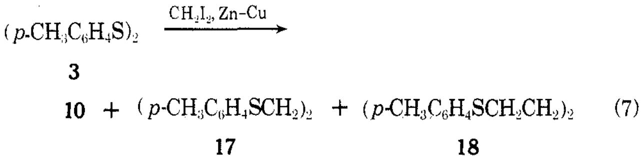
The ylide intermediate **16** is reminiscent of that in eq 3. If this view is correct, zinc iodide probably present in the reaction mixture should be an inhibitory influence because of its competition with **1** for the disulfide bond; indeed, addition of 1.5 molar proportions of zinc iodide (relative to disulfide **2**) reduced the usual yield of up to ~85% of thioformal **9** to 4–9%, and 3 molar proportions reduced it to 0%. Use of 1,2-dimethoxyethane–ether in the usual Simmons–Smith reaction rapidly and quantitatively precipitates zinc iodide;[2a] this approach promised to improve results of eq 4 by eliminating competition of zinc iodide, but use of a 1:1 mixture of these two ethers actually reduced the yield to 8% (NMR); perhaps the glycol ether simply competed too effectively with the disulfide bond for the reagent **1**.

In comparison of substituents, electron-donating groups were studied first. Di-*p*-tolyl disulfide (**3**) gave insertion product **10** in a yield of 50% by NMR and 33% by isolation. This yield was between the extremes for diphenyl disulfide and other disulfides discussed below, and the reaction of **3** thus was used to probe still further features of eq 4 and 6, with the results of a–c.

(a) One such feature is the possible role of homolysis, a pathway postulated (without evidence as yet) for insertion effected by rearrangement of ylides from a carbene and disulfides.[6] Irradiation with uv light reduced the yield of **10** from 48–50% to 10–17%; an increase would have been more consistent with homolysis. Passage of dry air, with oxygen as a radical scavenger, reduced the yield to 0%, a result consistent with intervention in a homolytic pathway but in heterolytic ones as well (it is worth adding that although dry air increases the yield of Simmons–Smith reactions in benzene,[7] the yield of the phenyl compound **9** decreased when air was passed from 13% in benzene to 5%). The results with air probably signify easily oxidizable intermediates, rather than free radicals. When the usual conversion to **9** in ether was repeated, with ESR spectra taken at 30-min intervals during 2 hr, no ESR signal for free radicals could be observed, although NMR showed that **9** had begun to form.[8] These experiments are not conclusive, but together they perhaps point more toward heterolysis than homolysis as the major pathway for eq 4.

(b) Tetrahydrofuran and diglyme, as alternatives to ether for preparing **10**, proved even worse than benzene (6% yield) probably for the reason suggested with the diether–ether mixture. As with **9**, results with **10** were best with reaction in ether for 24–30 hr with a **1**:**3** ratio of 1.5.

(c) Interestingly, GC–mass spectrometric study showed presence of products corresponding to insertion of both two and four methylene units (eq 7)



$$\underset{\mathbf{3}}{(p\text{-}CH_3C_6H_4S)_2} \xrightarrow{CH_2I_2,\ Zn\text{-}Cu} \mathbf{10} + \underset{\mathbf{17}}{(p\text{-}CH_3C_6H_4SCH_2)_2} + \underset{\mathbf{18}}{(p\text{-}CH_3C_6H_4SCH_2CH_2)_2} \quad (7)$$

each in less than 5% yield, along with the 33% of **10** isolated. The di-insertion product **17** also has been observed in the reaction of **3** with diazomethane.[9] The di-insertion product **17** could not be well separated from the mono-insertion product **10**, but the mass spectrum of the mixture was identical with the sum of the spectra of authentic **10** and **17**; a tetrainsertion product, presumed to be **18**, was separable by GC and showed a molecular ion. The bis(arylthio)methane probably is not an intermediate in these insertions, because when **9** was allowed to react with **1** under the usual conditions, although GC separated insertion products, none had either the mass spectrum of authentic 1,2-bis(phenylthio)ethane or the mass spectrometric pattern seen with the presumed **18** (the products perhaps were $C_6H_5SCH_2SCH_2C_6H_5$ and $C_6H_5SCH_2CH_2SCH_2C_6H_5$). Furthermore, treatment of the thioformal **10** itself gave no indication of **17** or **18** after GC–mass spectrometry.

With bis(2,3-dimethylphenyl) disulfide (**4**), a second effect was superimposed on electron donation. The yield of thioformal **11** was only 5% (NMR, isolation); 90–95% of **4** was recovered. This second effect is the steric hindrance afforded by an ortho substituent, presumably against formation of a bulky zinc-containing intermediate (*cf.* eq 6).

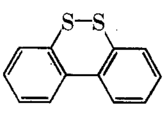
With bis(*p*-methoxyphenyl) disulfide (**5**), still a third effect appeared. The yield of bis(*p*-methoxyphenylthio)methane (**12**) was 25% both by NMR and isolation. The lower yield than usual (**2**, up to 85%; **3**, ~50%) is attributable to coordination of zinc species with the CH_3O moiety of **5**, which should place positive charge on the CH_3O moiety and make it a less effective electron donor; evidently, good characteristics of the S–S bond as an electron donor are crucial.

All three substituent effects (viz., electron donation, ortho hindrance, and Lewis type basicity) played a role with bis(2,4-dimethoxyphenyl) disulfide. Two good electron-donating groups are present, but one is in the ortho position and both are subject to coordination with zinc. Neither NMR nor isolation revealed any bis(2,4-dimethoxyphenylthio)methane; 90–95% of disulfide was recovered.

Neither bis(*N*,*N*-dimethylaminophenyl) disulfide (**6**) nor bis(*p*-aminophenyl) disulfide (**7**) did well, presumably because of coordination with zinc; no **13** or **14** could be isolated, although NMR showed yields of 13–16%.

Not surprisingly, electron-withdrawing substituents led to poor results. Bis(*p*-chlorophenyl) disulfide (**8**) gave **15** in only 5% yield (NMR, isolation), and reduction was marked (up to 16% of thiol and ~5% of methyl *p*-chlorophenyl sulfide). Bis(*p*-nitrophenyl) disulfide gave no bis(*p*-nitrophenylthio)methane (NMR, isolation); *p*-nitrothiophenol resulted (2–9%), but the nitro disulfide usually was recovered (63–93%). As with **2**, the Zn–Cu couple alone did not significantly reduce the nitro disulfide (3% of thiol), although this disulfide probably is the easiest of the group to reduce. *p*-Methoxyphenyl *p*-nitrophenyl disulfide merely disproportionated to the symmetrical disulfides.

The heterocyclic disulfide **19**, dibenzo[*c*,*e*]-*o*-dithiin, gave no monoinsertion product; GC–mass spectrometry indicated about 20% of a tri-insertion product. The alkyl and aralkyl disulfides di-*n*-propyl disulfide, and dibenzyl disulfide were recovered in 98% yield.



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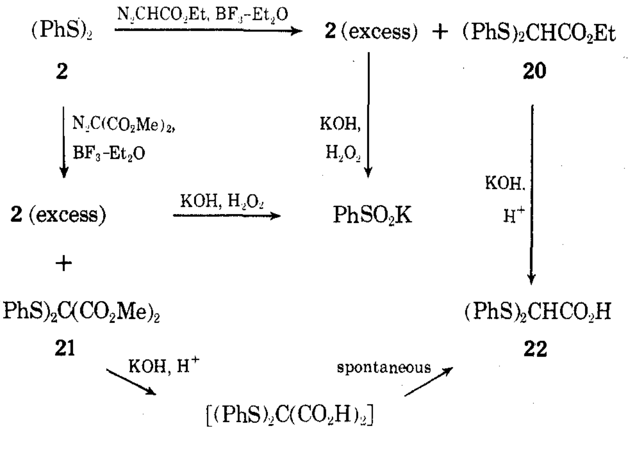
In sum, insertion of CH_2 into disulfides by the Simmons–Smith carbenoidal species succeeds best with aryl disulfides lacking substituents that are ortho, strongly electron withdrawing, or strongly basic in the Lewis sense.

Copper-catalyzed decomposition of diazoacetates to carbenoids is well known;[10] these are selective to a degree uncommon to carbenes.[10b] The only copper-associated carbenoid tried with disulfides is mentioned above.[3] Copper-catalyzed decomposition of ethyl diazoacetate in the presence of **2** apparently led to insertion (**20**, Scheme I) and also to other products. These efforts were discontinued when the mixture proved intractable and when BF_3-catalyzed insertion proved cleaner. Copper-catalyzed insertion of dimethyl diazomalonate with **2** gave **21** in a cleaner reaction than that of the diazoacetate but the BF_3-catalyzed reaction gave equivalent results (NMR), involved less vigorous conditions, and was more convenient.

Scheme I



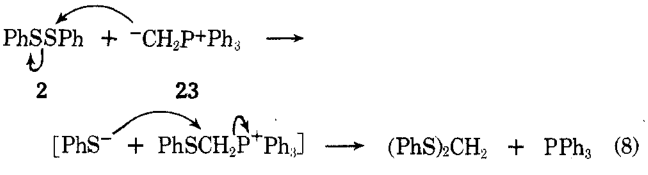
Carbenes. Reviews are available on carbenes (and carbenoids).[11a-d] Early in our work, there were only two reports of reactions of carbenes with disulfides,[12a,b] but others soon appeared.[6,9,12c] Several reported insertions like that of eq 1 with carbenes engendered thermally or photochemically.[6,9,12b,c]

On the other hand, insertions of the $CHCO_2Et$ moiety between the alkoxyl groups and methinyl carbon of orthoformates had been achieved catalytically using a diazoacetate.[13] The catalyst was boron trifluoride etherate, suggesting that this catalyst also might be effective for insertions using diazo esters with disulfides. Although such a reaction with a disulfide formally (and perhaps actually) would correspond to insertion of a carbene (cf. ref 13), it could also be cationic (diazonium and/or carbonium ion).[11e] Viewing the intermediate in such a reaction at least as a carbenoid is reasonable, since this loose term describes "... intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species ..." and since the term "... is very useful in the discussion of many methylene transfer reactions where the precise constitution of the reactive species has not been delineated".[11f]

In any event, insertion with ethyl diazoacetate and phenyl disulfide (**2**) did occur, proceeding best with 2 molar equiv of **2** (Scheme I). As with our earlier insertions, removal of unchanged disulfide was difficult, but **2** finally was removed using alkali and peroxide (Scheme I), a procedure that converts aryl disulfides to water-soluble products.[14] This procedure saponified **20** only partially, but completion of the saponification permitted isolation of pure **22** in 16% yield. The identity of **22** was established by comparison with authentic **22**. The BF_3-catalyzed reaction of a diazomalonate led after decarboxylation of the malonic acid to **22** (11% yield, Scheme I). The 11–16% of **22** isolated seems to represent only perhaps a third or a fourth of the insertion products **20** and **21** actually formed. Ando and coworkers in photolytic studies using dialkyl disulfides and dimethyl diazomalonate isolated insertion products corresponding to **21** in 2% yield.[6]

In the earliest study of disulfides with carbenes per se, Searles and Wann found that dichlorocarbene led to dichloromethyl alkyl disulfides. This reaction was general for alkyl disulfides containing β hydrogen atoms and led also to an alkene.[12a] Interestingly, the aryl disulfides **2**, **3**, and **5** were recovered (95–100%) when dichlorocarbene was generated in their presence by thermally induced decomposition of an equimolar amount of sodium trichloroacetate in 1:3 diglyme–tetrachloroethylene, a procedure based on a well-known one for forming cyclopropanes.[15] Evidently dichlorocarbene was formed, since carbon dioxide slowly evolved during about 4 hr under reflux. Perhaps a complex like **16** formed of the carbene and disulfide but, instead of rearranging, reverted to the carbene which then coupled to give tetrachloroethylene; it is also possible that aryl disulfides may simply be too weakly basic to form the complex.

Ylides.[16] The insertion shown by eq 8

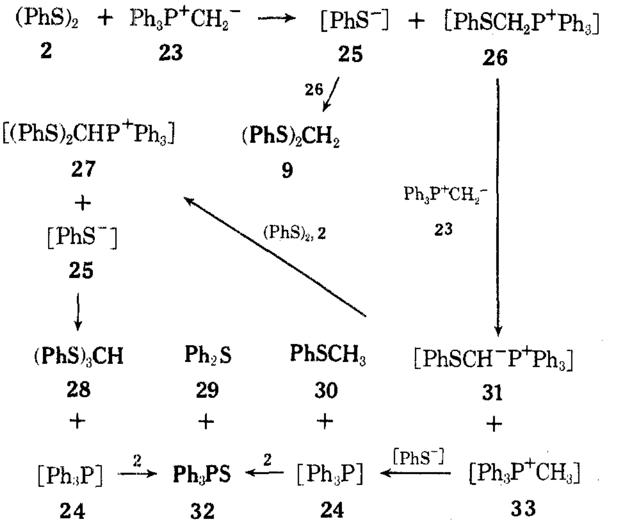


$$\underset{\mathbf{2}}{PhSSPh} + \underset{\mathbf{23}}{{}^{-}CH_2P^{+}Ph_3} \longrightarrow [PhS^{-} + PhSCH_2P^{+}Ph_3] \longrightarrow \underset{\mathbf{9}}{(PhS)_2CH_2} + \underset{\mathbf{24}}{PPh_3} \quad (8)$$

seemed a reasonable outcome for reaction of the ylide **23** with disulfide **2** (the phosphine **24** and **2** presumably would subsequently form diphenyl sulfide and triphenylphosphine sulfide).[17] Attempted reaction in boiling ether led only to recovery of 95–100% of **2**. In diglyme at 130° **2** reacted during 24 hr (at 100°, 98% recovery), but only a trace of the insertion product **9** was isolated. Scheme II shows the products (boldface), along with reactions that rationalize their formation. Attack of **25** on **26** to give **9** and the phosphine **24** clearly is minor (~0.3% of **9**). Instead, in the major course of reaction, **26** (perhaps as a tight ion pair with **25**) is considered to lose a proton to ylide **23**, thereby forming a new ylide **31**, along with **33**. The new ylide **31** then consumes more disulfide **2** and leads through **25** and **27** to tris(phenylthio)methane (**28**). The ylide **23**, having abstracted the proton, becomes a methylating agent (**33**) that produces **24** and **30**. Finally, triphenylphosphine (**24**) desulfurizes **2**,[17] giving **29** and **32**. Equation 9 summarizes

$$\underset{\mathbf{2}}{4(PhS)_2} + \underset{\mathbf{23}}{2Ph_3P^{+}CH_2^{-}} \longrightarrow \underset{\mathbf{28}}{(PhS)_3CH} + \underset{\mathbf{29}}{2Ph_2S} + \underset{\mathbf{30}}{PhSCH_3} + \underset{\mathbf{32}}{2Ph_3PS} \quad (9)$$

Scheme II



these reactions. Based on eq 9 in various reactions tris(phenylthio)methane (**28**) was isolated in up to 64% yield and methyl phenyl sulfide (**30**) in up to 6% yield. Diphenyl sulfide (**29**) was not sought since the phosphine sulfide (**32**) was isolated. Thiophenol was isolated in yields up to 28%, presumably reflecting incomplete reaction of the thiolate ion **25** involved at several stages. When the tolyl disulfide **3** was used with **23**, no indication was seen of interchange of tolyl and phenyl groups.

Before Scheme II was developed, it seemed likely that the tris sulfide **28** had formed by abstraction of a proton from the insertion product **9** by the ylide **23**, followed by attack of the resulting carbanion of **9** on **2**. Three pieces of contrary evidence were adduced. (1) When equimolar amounts of **9** were treated with ylide **23** and disulfide **2**, NMR indicated no loss of **9**. (2) Treatment of **9** with ylide **23** led to no detectable methylation of **9** (95% recovery). (3) Treatment of **9** with ylide **23** at 30° for 2 hr, followed by quenching with D_2O, led neither to loss of intensity of the NMR methylene signal (relative to a standard) nor to the splitting expected if deuterium had replaced hydrogen; hence **23** is unable to abstract a proton from **9** readily.

The reaction also proceeds with an alkyl disulfide. When *n*-propyl disulfide was subjected to the reaction, tris(*n*-propylthio)methane was isolated in 17% yield (38–78% by NMR); 1-propanethiol (4%) and **32** also were isolated.

Nitrenes.[11b,18a] *p*-Azidobenzonitrile thermolyzed with **2** with and without copper powder (up to 48 hr, ~130°) led only to recovery of the **2** (89%) and gave no indication of much S–N bonding (<2% by reaction with thiophenol). Photolysis (30 hr) led to 43–45% recovery of each starting material, with no evidence of S–N bonding. Heating of *p*-toluenesulfonyl azide and **2** at 155° for 5 hr also gave no evidence for S–N bond formation. The conditions required for reaction according to eq 10 thus seemed likely to be so extreme that there would be little chance for survival of sulfenamides. Indeed, insertion products actually might have been destroyed by reactions like that of eq 11. Dialkyl disulfides react with methyl azidoformate but give alkylthio- and alkyldithiocarbamates, $RSNHCO_2Me$ and $RSSNHCO_2Me$, respectively.[18b]

$$(RS)_2 + R'N_3 \longrightarrow (RS)_2NR' + N_2 \qquad (10)$$

$$2(RS)_2NR' \longrightarrow 2(RS)_2 + R'N{=}NR' \qquad (11)$$

Experimental Section[19]

Materials. A. Disulfides. *p*-Nitrophenyl *p*′-methoxyphenyl disulfide was prepared by the reaction of *p*-nitrobenzenesulfenyl chloride and *p*-methoxythiophenol. The sulfenyl chloride was prepared by condensing Cl_2 (0.9 g, 12.7 mmol) using Dry Ice–acetone and then allowing it to volatilize spontaneously (ca. 20 min) upon removal of cooling into a stirred solution of bis(*p*-nitrophenyl) disulfide (3.7 g, 12.0 mmol) in 75 ml of CH_2Cl_2 maintained at −20°. The resulting solution was added (ca. 30 min) to a stirred solution of *p*-methoxythiophenol (3.36 g, 24 mmol) in 75 ml of CH_2Cl_2. The mixture was allowed to warm to ~25° with stirring and then was washed with H_2O, 5% aqueous $NaHCO_3$, and H_2O to neutrality. Drying and removal of solvent gave the unsymmetrical disulfide as a viscous oil (2.50 g, 36%). TLC showed one spot using CH_2Cl_2, benzene, benzene–Me_2CO (2:1), EtOAc, petroleum ether, or EtOH; NMR (CCl_4) δ 6.4–7.9 (m, 8, Ph), 3.6 (s, 3.2, CH_3). The product was not further purified to avoid possible disproportionation.

Anal. Calcd for $C_{13}H_{11}NO_3S_2$: C, 53.27; H, 3.76; S, 21.84. Found: C, 53.34; H, 4.24; S, 21.23.

Bis(2,3-dimethylphenyl) Disulfide (**4**, obtained by oxidizing the thiol, prepared by diazotizing the corresponding amine and treating with a xanthate) was kindly provided by L. H. Brannigan: mp 98–98.5°; NMR (CCl_4) δ 6.9–7.4 (m, 6, PhH), 2.3 (s, 6, CH_3), 2.25 (s, 6, CH_3).

Anal. Calcd for $C_{16}H_{18}S_2$: C, 70.07; H, 6.56; S, 23.35. Found: C, 70.14; H, 6.65; S, 23.27.

The other disulfides used have been reported previously; melting points before use were in good agreement with reported values (±2°). The dimethylamino disulfide **6** was prepared using sulfur monochloride and *N,N*-dimethylaniline,[20] mp 118–119° (lit.[20] mp 118°); use of formic acid–formaldehyde with bis(*p*-aminophenyl) disulfide, in a modified Leuckart reaction,[21] gave **6** in much lower yield and purity. Bis(2,4-dimethoxyphenyl) disulfide was prepared by reducing the sulfonyl chloride to the thiol and oxidizing with I_2,[22,23a] mp 115–116° (lit.[23a] mp 113–115°). Dibenzo[*c,e*]-*o*-dithiin (**19**) was prepared by reducing 2,2′-biphenyldisulfonyl chloride with HI,[1a] mp 111.5–112° (lit.[1a] mp 112–113°). All other disulfides (purified as stated) were either commercial products or were prepared by oxidizing commercially available thiols with I_2 (**2, 3, 5, 7, 8**, and others not numbered).

B. Bis(arylthio)methanes and 1,2-Bis(arylthio)ethanes. Preparation of bis(phenylthio)methane (**9**), based on a general procedure,[4] is illustrative. Addition of CH_2I_2 (85 mmol) during ~15 min to thiophenol (170 mmol) in EtOH (75 ml) containing 170 mmol of NaOH led to an exothermic reaction. The mixture was stirred for 2 hr and diluted with H_2O (25 ml). An Et_2O extract gave **9** in 78% yield; mp after recrystallization (EtOH), 34–35° (lit.[4] mp 36°). Other bis(arylthio)methanes prepared similarly were **10** (oil, lit.[4] mp 30°); **11** [mp 58–59°; NMR (CCl_4) δ 6.9–7.3 (m, 6, Ph), 4.1 (s, 2, CH_2), 2.2 (s, 6, CH_3), 2.1 (s, 6, CH_3)]; **12** [mp 68–69° (lit.[23b] mp 66–67°)]; and **15** [mp 38–39° (lit.[23b] mp 39–39.5°)].

Preparation of 1,2-bis(*p*-tolylthio)ethane (**17**) and 1,2-bis(phenylthio)ethane was identical with that of the bis(arylthio)methanes, except in use of $Br(CH_2)_2Br$ instead of CH_2I_2: **17**, mp 79–79.5° (lit.[4] mp 80°); 1,2-bis(phenylthio)ethane, mp 68–69° (lit.[4] mp 69°).

C. Miscellaneous. *p*-Azidobenzonitrile[24] had mp 64–64.5° (lit.[25] mp 70°), and *p*-toluenesulfonyl azide[26] was used as an oil (lit.[18] mp 24–26°). Bis(phenylthio)acetic acid (**22**) was prepared, essentially as reported,[27] from sodium dichloroacetate and sodium benzenethiolate; after recrystallization to constant melting point, the melting point was 103–104° (lit.[27] mp 104°). Tris(phenylthio)methane (**28**) was kindly provided by D. L. Tuleen, mp 39–40° (lit.[28] mp 40°). Zinc iodide was prepared as described (method II).[29] All other substances were obtained commercially.

Reactions of the Simmons–Smith Reagent (1) with Diaryl Disulfides. The reaction of **1** with diphenyl disulfide (**2**) is illustrative. A slurry of **1** was prepared, using a reported procedure,[30] by adding Zn dust (1.96 g, 30 mmol) to a nearly boiling solution of $Cu(OAc)_2$ (0.23 g, 1.25 mmol) in glacial AcOH (30 ml). After 5 min, the AcOH was decanted from the Zn–Cu couple. The couple was washed repeatedly with anhydrous Et_2O until no trace of AcOH was evident (by odor) and then was transferred to the reaction flask and stirred in Et_2O (100 ml). About half of the CH_2I_2 (2.44 ml, 30 mmol) was added dropwise during ~15 min (exothermic reaction). The disulfide **2** (4.36 g, 20 mmol) in 30 ml of Et_2O was added to the remainder of the CH_2I_2, and this mixture then was added during ~15 min with good stirring. The mixture then was stirred vigorously for 24 hr under reflux. Removal of solid by filtration, and evaporation of solvent and excess CH_2I_2, then left the crude reaction product.

Products were isolated by column chromatography,[19] with treatment by $LiAlH_4$ in Et_2O being used if the bis(arylthio)methane did not separate cleanly [**9**, **10**, and (occasionally) **12**]. When $LiAlH_4$

was necessary, a clear Et_2O solution was added dropwise to the fraction in Et_2O (until excess $LiAlH_4$ could be shown by gassing when a few drops were added to wet alcohol), and the solution was heated under reflux for 2 hr; excess $LiAlH_4$ then was hydrolyzed, and thiol was washed out with 10% aqueous NaOH. Products were identified by melting point, mixture melting point, and congruency of NMR spectra with authentic samples.

For the NMR assays of incompletely purified products, based on relative integrals of aryl and $-SCH_2S-$ protons,[1c] the validity of the method was checked by analysis of standard mixtures containing 25, 50, and 75% of **9** with **2**; the results, respectively, were 23, 48, and 73%. Insertion products **13** and **14** were not isolated, and the $-SCH_2S-$ signal of δ 4.1–4.5 was used in estimating percent composition [a reasonable assumption since this signal varied from δ 4.0 to 4.2 for six other bis(arylthio)methanes].

For the inverse mode (i.e., when the reagent **1** was added to the disulfide), the Zn–Cu couple was made as before, and CH_2I_2 then was added to the couple in Et_2O. Solid was removed by a quick gravity filtration, and the resulting clear solution was added during 15 min to a solution of **2** in Et_2O. Other procedures were as before.

Cu-Catalyzed Reactions of Diazo Esters with Diphenyl Disulfide (2). According to a general procedure for reaction of diazoacetates with various substrates,[10a] a mixture of 0.79 g (5.0 mmol) of dimethyl diazomalonate, 2.18 g (10.0 mmol) of **2**, and 0.16 g (1.0 mmol) of freshly dried anhydrous $CuSO_4$ was heated at 90° under nitrogen until N_2 evolution ceased (~30 min). The mixture was cooled and agitated with Et_2O. The Et_2O extract was filtered and concentrated to give 2.4 g of crude **21** as an oil that appeared by NMR to be composed of about 17% of **21** (for an estimated yield of 24% of **21**). This crude **21** was roughly equivalent by NMR to products obtained from the BF_3-catalyzed decomposition described below.

Essentially the same procedure of reaction was used with ethyl diazoacetate (100 mmol), **2** (200 mmol), and $CuSO_4$ (2 mmol). Crude products resulted that appeared to consist of a little diethyl fumarate and maleate, one unidentified material with NMR δ 3.4 (s), and another with δ 5.7 (s). A component with δ 4.65 (s) was believed to be the insertion product **20**, but it could not be separated cleanly by column chromatography or preparative TLC from other products; in the best reaction, NMR suggested that this presumed **20** amounted to 25% of the product (~25% yield).

BF_3-Catalyzed Reactions of Diazo Esters with Diphenyl Disulfide (2). A. Ethyl Diazoacetate. In a modification of a reported procedure for BF_3-catalyzed reactions of diazoacetates,[13] ethyl diazoacetate (0.57 g, 5.0 mmol) was added dropwise during ~3 min to a mixture of **2** (2.18 g, 10.0 mmol) and boron trifluoride etherate (0.5 ml). Immediate evolution of N_2 occurred. The liquid then was heated at 40° for 2 hr to assure decomposition of the diazoacetate (loss of the characteristic diazo frequency at ~2150 cm^{-1}). The mixture cooled to ~25°, mixed with H_2O (20 ml), and extracted well with Et_2O. The extract was dried and concentrated to give 2.6 g of oil [NMR of the δ 4.65 peak suggested that this oil contained 34% of the insertion product **20**, ethyl bis(phenylthio)acetate, corresponding to a yield of 58%].

In most of these diazoacetate experiments, the δ 3.4 peak seen in the copper-catalyzed reaction was present, but the δ 5.7 peak was absent. In experiments with varied ratios of disulfide **2** to diazoacetate, a 2:1 ratio most favored the δ 4.65 peak and hence presumably the formation of **20**; a 1:2 ratio gave about equal intensity of the δ 3.4 and δ 4.65 peaks and a 1:1 ratio greatly increased the δ 3.4 peak. These results were the basis of the 2:1 ratio used above of **2** to diazoacetate.

Column chromatography purified the crude **20** considerably, but much **2** remained. Efforts to remove this **2** by reduction with Zn–AcOH or Ph_3P–H_2O caused loss of the δ 4.65 peak, and oxidation with peroxide or cleavage with ethanolic base also were unsatisfactory. Finally, an effective means of removing **2** without apparent damage to the **20** was based on the report that base-induced cleavage of diaryl disulfides, in the presence of H_2O_2, converts them in good yield to (water-soluble) sulfinic acid salts.[14] Subsequent further treatment with base was needed for complete saponification of **20**, however. In this procedure, part of the crude **20** (1.0 g) was assumed to be all disulfide (i.e., to represent 4.6 mmol of **2**) and was dissolved in 20 ml of EtOH, to which was added KOH (0.52 g, 9.2 mmol) in H_2O (30 ml) and 30% H_2O_2 (1.56 g, 13.8 mmol). The mixture was heated at 35° for 18 hr with stirring. It then was acidified with 10% HCl, and the EtOH was evaporated. An Et_2O extract of the aqueous residue was washed twice with H_2O to remove most of the benzenesulfinic acid, dried, and evaporated to give an oil. This partially saponified **20** then was heated under reflux for 18 hr in EtOH (20 ml) containing 1.03 g (18.4 mmol) of KOH. Evaporation of EtOH and acidification, followed by reprecipitation from aqueous $NaHCO_3$ with several recrystallizations (H_2O), gave 0.17 g (16%) of **22**, mp 101–102°. Further recrystallizations gave **22** with a constant melting point of 102–103°, which had ir and NMR spectra congruent with those of authentic **22**, bis(phenylthio)acetic acid; the melting point was undepressed by authentic **22**[27] (lit.[27] mp 104°).

B. Dimethyl Diazomalonate. The procedure of A for the diazoacetate was duplicated using dimethyl diazomalonate (0.79 g, 5.0 mmol), **2** (2.18 g, 10.0 mmol), and boron trifluoride etherate (0.5 ml). The Et_2O extract yielded 2.4 g of oil [NMR of the OCH_3 peak at δ 3.65 suggested that this oil contained 17% of the insertion product **21**, dimethyl bis(phenylthio)malonate, corresponding to a yield of 23%]; in several other experiments, the range of percent composition for **21** was 27–47%.

In various preparations of **21**, all of which were done with a 2:1 ratio of **2** to diazomalonate, there were present a little tetramethyl 2,3-dicarboxymaleate, and a compound with δ 4.3. Up to 50% of **2** could be recovered in some instances. Column chromatography effected partial separation of **2**, but the removal of **2** by conversion to benzenesulfinic acid still was necessary, with isolation of the acid **22** as in A. For this conversion of **21** to **22**, part of **21** (1.0 g, 4.6 mmol had the product been pure **2**) was treated in 20 ml of EtOH, as in A, with 0.52 g (9.2 mmol) of KOH in 30 ml of H_2O and 1.56 g (13.8 mmol) of 30% H_2O_2. Complete saponification of the partially saponified **21** then was achieved as in A, with 1.03 g (18.4 mmol) of KOH in 20 ml of EtOH. Acidification and reprecipitation from aqueous base with acid and recrystallizations gave 0.1 g (11%) of the acid **22**, mp 100–101°. Further recrystallization gave **22** with a constant melting point of 102–103°, which had ir and NMR spectra congruent with those of both authentic **22**[27] and the **22** from A; the melting point was not depressed by either of these other two samples.

Reaction of Methylenetriphenylphosphorane (23) with Aryl and Alkyl Disulfides. The reaction of diphenyl disulfide (**2**) with **23** exemplifies the general procedure. The ylide **23** was formed by addition of triphenylmethylphosphonium bromide (3.57 g, 10.0 mmol) to a diglyme solution (100 ml, dried with $LiAlH_4$ and freshly distilled) containing *n*-butyllithium (in hexane, 10 ml, 10.0 mmol) under N_2; the solution became orange, signifying formation of **23**. The mixture then was heated at 130° for 1 hr, after which **2** (2.18 g, 10.0 mmol) dissolved in 10 ml of diglyme was added dropwise during 30 min. The solution then was heated for 24 hr at 130° under N_2, cooled to 25°, and poured into H_2O (500 ml). The aqueous mixture was extracted well with Et_2O, and the Et_2O extract was washed well with H_2O and dried. Evaporation of the Et_2O gave an oily mixture. In various experiments, NMR suggested that the ratio of **28** to **30** in the mixture varied from 9:1 (the present experiment) to 0.7:1; **9** never was seen in more than trace amounts.

Upon chromatography of part of the crude product using Brinkmann silica gel G, benzene eluted three products (in the order of mention, with yields in parentheses being based on eq 9): **30**, methyl phenyl sulfide (6%); **9**, bis(phenylthio)methane (0.3%, based on eq 8); and, **28**, tris(phenylthio)methane (64%), mp 39°. The identities of **9**, **28**, and **30** were established by congruence of NMR spectra with those of authentic samples; the mixture melting point of **28** was undepressed by authentic **28**. The yields varied with the conditions of reaction. In other experiments, **32**, triphenylphosphine sulfide, crystallized from the crude product and was identified by NMR and melting point.

Acidification of the water-diglyme raffinate and extraction with Et_2O separated thiophenol formed; titration with I_2 showed the yield to be 28%.

The reaction of **23** with di(*n*-propyl) disulfide was carried out using similar molar proportions and similar conditions. Tris(*n*-propylthio)methane was identified, after distillation of the products, by boiling point and NMR (congruency with authentic material prepared by the well-known method of heating the thiol with chloroform; δ CH, 4.7). Triphenylphosphine sulfide (**32**) was identified by NMR and melting point. 1-Propanethiol was estimated by acidification of the basic reaction mixture, extraction, and titration with I_2.

Registry No.—**2**, 882-33-7; **3**, 103-19-5; **4**, 55990-91-5; **5**, 5335-87-5; **6**, 5397-29-5; **7**, 722-27-0; **8**, 1142-19-4; **9**, 3561-67-9; **19**, 230-26-2; **23** (uncharged form), 3487-44-3; **23** (charged form), 19493-09-5; *p*-nitrophenyl *p*′-methoxyphenyl disulfide, 20168-74-5; *p*-nitrobenzenesulfenyl chloride, 937-32-6; *p*-methoxythiophenol, 696-63-9; bis(2,4-dimethoxyphenyl) disulfide, 55990-92-6; CH_2I_2, 75-11-6; thiophenol, 108-98-5; $Br(CH_2)_2Br$, 106-93-4; dimethyl diazomalonate, 6773-29-1; ethyl diazoacetate, 623-73-4; triphenylmethylphosphonium bromide, 1779-49-3; di(*n*-propyl) disulfide, 629-19-6.

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Nucleophilic Cleavage of the Sulfur–Sulfur Bond by Phosphorus Nucleophiles. III. Kinetic Study of the Reduction of a Series of Ethyl Aryl Disulfides with Triphenylphosphine and Water[1]

Larry E. Overman*[2a] and Stephen T. Petty[2b]

Department of Chemistry, University of California, Irvine, California 92664

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A stopped-flow kinetic study of the reaction of a series of ethyl substituted-phenyl disulfides (2) with triphenylphosphine (Ph_3P) in 50% dioxane–water at pH 13.3 is reported. This reaction results in reduction of the disulfide to yield the corresponding benzenethiol, ethanethiol, and triphenylphosphine oxide. Triphenylphosphine sulfide is not formed. In analogy with our previous study of the reaction of symmetrical aryl disulfides with Ph_3P a two-step mechanism is suggested. At pH 13.3 the first step is rate determining. A plot of log k_1 against σ yields a ρ value of 1.76 (standard deviation 0.07). The substituent effect data are interpreted to indicate that some negative charge is developed on both sulfur atoms in the transition state as bond making is somewhat advanced over bond breaking.

We recently reported[1] evidence to indicate that the reduction of symmetrical aryl disulfides with triphenylphosphine (Ph_3P) in aqueous dioxane involves at least two steps (Scheme I). The rate-determining step of this redox reaction was shown to be pH dependent. At both low and high pH, nucleophilic attack by Ph_3P on the S–S bond to form an intermediate thioalkoxyphosphonium cation (1) is rate limiting, while at intermediate pH the reversal of the first step becomes important and the reaction is kinetically more complex.[1] Based primarily on the large sensitivity of the first step of Scheme I to the electron-withdrawing nature of the disulfide substituents ($\beta = -1.02$, $\rho = 2.94$) it was tentatively suggested that nucleophilic attack by the phosphine occurs via a transition state in which negative charge is developed on both sulfur atoms, and that thus the sulfur undergoing attack is partially valence expanded as

Scheme I

$$\mathrm{Ph_3P} + \mathrm{ArSSAr} \rightleftharpoons \underset{\mathbf{1}}{\mathrm{Ph_3\overset{+}{P}{-}SAr}} + \mathrm{ArS^-}$$

$$\mathrm{Ph_3\overset{+}{P}{-}SAr} + \mathrm{H_2O} \longrightarrow \mathrm{Ph_3PO} + \mathrm{ArS^-} + 2\mathrm{H^+}$$