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Sulfenylation Reactions with Disulfides in the Presence of CCl_4/Base$^+$

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ABSTRACT

Sulfenylation of active methylene compounds with disulfides and CCl_4/base, proceeding in two steps, gives rise to more than 50% of the introduced sulfur component due to the reoxidation of the thiolate into the starting disulfide. Depending on the reaction conditions, arylacetonitriles and diaryl disulfides react to form mono- or bis-sulfenylated products. By use of this method, a number of previously unknown α, α-bis-sulfenylated nitriles were prepared.

INTRODUCTION

The reaction of thiols with CCl_4 in the presence of a base, such as NEt_3, NaOH, or NaOEt, is one possibility for the mild oxidation of the thiols into the corresponding disulfides. Aryl thiols, in general, give better yields than alkyl thiols [2]. By treating other protic nucleophiles, HNu, with thiols and CCl_4 under comparable conditions, a sulfur-element bond formation can be observed (Equation 1).

$$RSH + HNu + CCl_4 \xrightarrow[-\text{base}\cdot HCl]{\text{base}} RS-Nu + CHCl_3 \qquad (1)$$

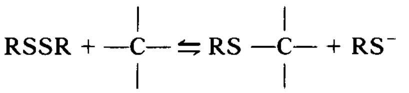
Gas chromatographic investigations have proven that this sulfur-element bond is not formed in a direct reaction between the thiol and the protic nucleophile. The thiol is completely oxidized to the disulfide before the sulfenylated species are formed [3]. Therefore, the disulfides are the real sulfur transfer reagents.

Active methylene ketones, such as acetylacetone (Hacac) and ethyl acetoacetate, can be sulfenylated by dialkyl-, diaryl-, and thiuramdisulfides according to Equation (2) in the presence of CCl_4/base [3–5].

$$RSSR + 2\,CH_3C(O)CH_2COR^1 \xrightarrow[\substack{-CHCl_3\\ -\text{base}\cdot HCl}]{CCl_4/\text{base}} 2\,CH_3C(O)CH(SR)COR^1 \qquad (2)$$

$$R^1{=}CH_3,\ OC_2H_5$$

The preparation of thioethers by the reaction of disulfides with carbanions is already known (Equation 3) [6–8].



$$RSSR + -\overset{|}{\underset{|}{C}}- \rightleftharpoons RS-\overset{|}{\underset{|}{C}}- + RS^- \qquad (3)$$

This equilibrium contains two disadvantages:

1. Because of simultaneous RS^--formation, not more than 50% of the "disulfide sulfur" can be converted into the thioether.
2. The reductive cleavage of the resulting carbon-sulfur bond by the thiolate anions (reverse reaction) will decrease the yield or completely suppress the sulfenylation reaction.

For Part 4, see Reference [1].
Part 5, CCl_4 as Mild Oxidant in Sulfur Chemistry.
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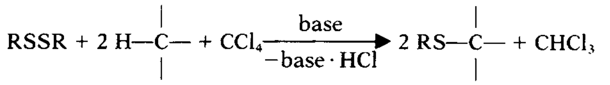
RESULTS AND DISCUSSION

In a general way, the sulfenylation of protic nucleophiles with disulfides and CCl_4/base may be summarized according to Equation (4):



$$\mathrm{RSSR} + 2\,\mathrm{H{-}}\overset{|}{\underset{|}{\mathrm{C}}}{-} + \mathrm{CCl_4} \xrightarrow[-\mathrm{base\cdot HCl}]{\mathrm{base}} 2\,\mathrm{RS{-}}\overset{|}{\underset{|}{\mathrm{C}}}{-} + \mathrm{CHCl_3} \qquad (4)$$

The thioether/trichloromethane ratio is always observed to be 1 : 1, but there is no proof for the mechanism of reaction, especially the interactions involving the CCl_4.

One possible way would entail the initial formation of a donor-acceptor complex between the disulfide and the CCl_4. Thus, one of the sulfur atoms could be attacked more easily by the nucleophile. Complexes of disulfides with tetracyanoethylene [9] and iodine [10] are already known and have been characterized by bathochromic shifts of the UV/VIS-absorptions compared with the starting materials. Iodine as the weaker acceptor only shows interactions with dialkyl disulfides; a Ph_2S_2/I_2-complex could not be detected [11]. We have investigated solutions of Ph_2S_2 and CCl_4 in DMF using different concentrations, but we could not find any new absorptions between 360 and 600 nm. In addition, electrochemical measurements of solutions of dialkyl and diaryl disulfides in acetonitrile also did not give any indication for the formation of those types of intermediates [1].

By means of UV/VIS spectroscopic observations of the reaction of acetylacetone (Hacac) with 5,5′-dithiobis(2-nitrobenoic acid), ELLMAN's reagent [12,13], we were able to show that the S–S bond is split in the first step by nucleophilic attack of the carbanion. Then, the formed thiolate anion is reoxidized by CCl_4 to the corresponding disulfide, which can react with the acac$^-$-ion again (Equations 5 and 6).

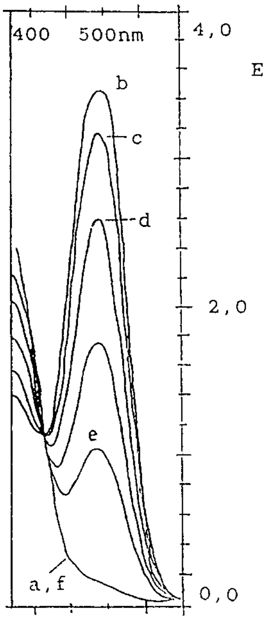
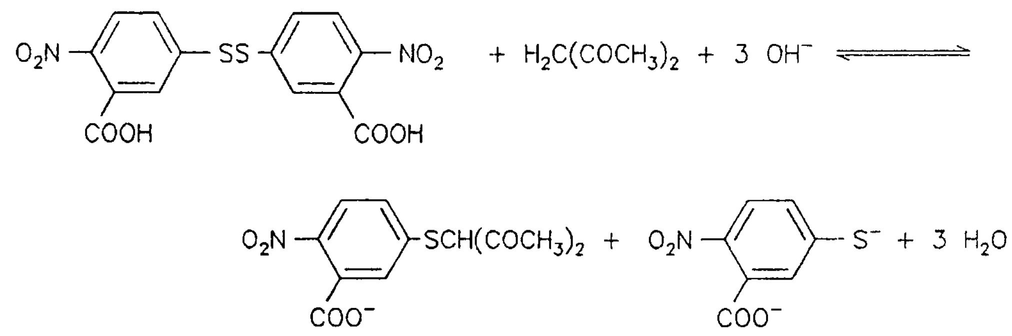


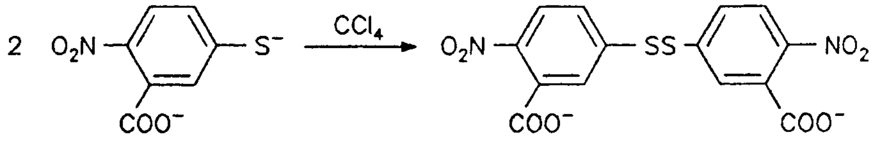
FIGURE 1 UV/VIS spectra of the reaction mixture according to Equations 5 and 6: (a) Hacac + NaOH in DMF; (b) Hacac + NaOH + disulfide; (c)–(f) after CCl_4 addition. (c) 0.5 min, (d) 1.0 min, (e) 2.0 min, (f) 3.5 min.

The formation (Equation 5) and oxidation (Equation 6) of the arylthiolate anion can easily be followed by UV/VIS-spectroscopy because of the intense absorption maximum at λ_{max} = 491 nm (DMF).

Acetylacetone and NaOH were dissolved in DMF (a) and a solution of the disulfide in DMF was added (b). Immediately, an intense absorption could be observed (formation of the thiolate anion, see Equation 5). After the addition of CCl_4 (c–f), the mentioned signal completely disappeared within 3.5 minutes. This is due to the fact that the



(5)



(6)

chromophoric ArS^--ion was reoxidized to the disulfide and so removed from the equilibrium.

Therefore, we came to the conclusion that sulfenylation reactions using disulfides in the presence of CCl_4/base proceed in two steps:

1. Nucleophilic attack of the carbanion at the disulfide sulfur-sulfur bond with the formation of a thioether and the thiolate anion.
2. Oxidation of the thiolate by CCl_4.

As a consequence of this thiolate oxidation to the starting disulfide, the equilibrium (see Equation 3) is shifted toward the sulfenylated species. Furthermore, the sulfur component may be utilized more than 50%, since the nucleophilic RS^--ions, which can attack and cleave the carbon-sulfur bond, are removed by this reaction.

In continuation of former investigations [3–5], we were interested in extending our concept of sulfenylation reactions with disulfides to other active methylene compounds. The reaction of phenylacetonitrile with disulfides using the common sulfenylation conditions (5 hours, 65°C) gives the α-cyano-thioethers only in low yields (Equation 7).

$$2\,PhCH_2CN + RSSR + CCl_4 \xrightarrow[-base\cdot HCl]{65°C,\ base} 2\,PhCH(SR)CN + CHCl_3 \qquad (7)$$

R =	Me	Et	Pr	Ph
(%)	18	5	5	20

At 0°C, however, another behavior is observed. A geminal bis-sulfenylation dominates and leads to the dithioacetals of phenylglyoxylic acid nitrile (Equation 8).

$$PhCH_2CN + RSSR + CCl_4 \xrightarrow[-base\cdot HCl]{0°C,\ base} PhC(SR)_2CN + CHCl_3 \qquad (8)$$

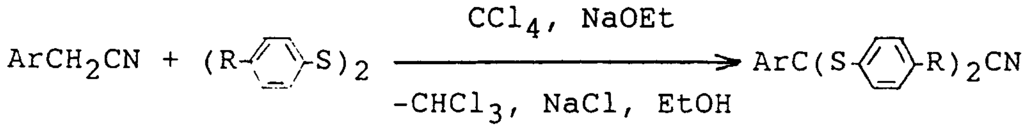
	R	Yield (%)	mp (°C)
1a	Ph	60.5	75–76
1b	4-ClC_6H_4	65	106
1c	$(CH_2)_4\,NC(S)$	8	124–125

In the case of the dialkyl disulfides, only traces of the monosulfenylated nitriles could be detected. The common method for the preparation of dithioacetals consists in the reaction of ketones (1 mole) with thiols (2 moles). Only one example for such a bis-sulfenylation of the phenylglyoxylic acid nitrile has been described (Equation 9) [14]; other reactions failed.

$$PhC(O)CN + 2\,EtSH \xrightarrow{ZnCl_2,\ 0°C,\ 6d} PhC(SEt)_2CN + H_2O \qquad (9)$$

With the described method, the sulfenylation of arylacetonitriles with disulfides in the presence of CCl_4/base to the corresponding dithioacetals occurs in good yields under mild conditions. The α-bis(dithiocarbamoyl) phenylacetonitrile is of special interest, since a reaction according to Equation 9 is not practicable because of the instability of the free dithiocarbamic acid [15].

The acidity of the methylene group sensitively depends on the different substituents R. Our interest was to study the influence of a higher CH-acidity caused by the introduction of electronegative groups at the reaction site mentioned above. According to Equation (10), a number of different arylacetonitriles were bis-sulfenylated by various diaryl disulfides.



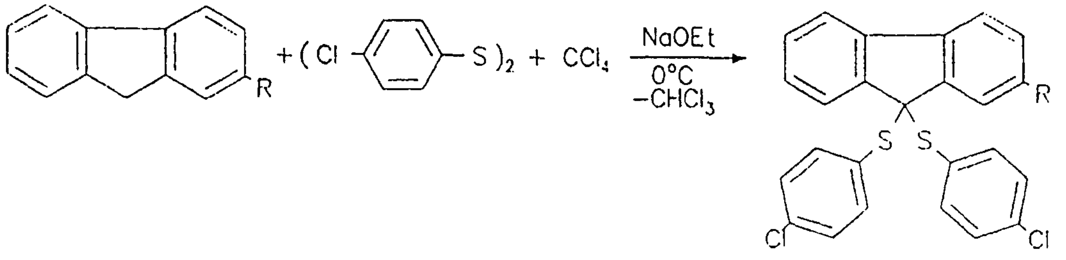
(10)

Ar		Yield (%) R = H		R = Cl
Ph	**1a**	60.5	**1b**	65
4-ClC_6H_4	**2a**	36	**2b**	71
4-$O_2NC_6H_4$		—		—
1-naphthyl	**3a**	15	**3b**	40

The introduction of a nitro-group into the para-position, on one hand, increases the CH-acidity but, on the other hand, decreases the nucleophilicity of the thiolate intermediate because of the larger delocalization of the negative charge. Thus, the carbanion is not able to cleave the sulfur-sulfur bond, and consequently, no sulfenylated product is observed.

The lower yields using 1-naphthylacetonitrile are due to both the reduced nucleophilicity and the influence of steric factors. In one case, a monosulfenylated product **3c** was also formed in a small amount. If diphenyl disulfide and the phenylacetonitrile are mixed at a molar ratio of 1:2, a non-stoichiometric one (see Equation 10), a mixture of the dithioacetal and the corresponding diphenylfumaric dinitrile results. Starting with equimolar amounts of the reagents, this dinitrile was observed only as a minor by-product.

The described bis-sulfenylation is not restricted to aromatic nitriles. Bis(4-chlorophenyl) disulfide, with fluorene and its 2-nitro-derivative, gives the corresponding 9,9-bis-sulfenylated products (Equation 11).

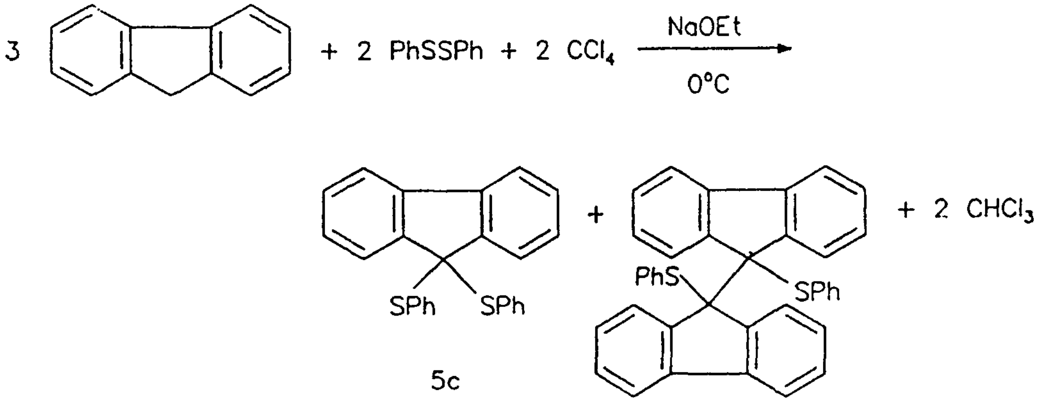


5a R = H (39%)

5b R = NO_2 (12%)

(11)

Compared with the unsubstituted fluorene, the reduced nucleophilicity of the 2-nitro-substituted carbanion causes an essentially lower yield. In this case, also, 9,9'-bifluorenylidene results as a red, high melting by-product. With diphenyl disulfide, a mixture of the expected dithioacetal **5c** and 9,9'-diphenylthio-9,9'-bifluorene **5d** (Equation 12) is formed.



5c

5d

(12)

2-nitrofluorene does not react with Ph_2S_2 in the presence of a base; only the formation of 9,9'-bifluorenylidene **5e** could be observed.

Successful dithioacetal formations obviously essentially depend on the following two factors concerning the active methylene species:

1. A pK_a value of ca. 20.
2. A carbanion nucleophilicity which is sufficient for the sulfur-sulfur bond cleavage.

Investigations related to this subject are being continued.

EXPERIMENTAL

Melting points are uncorrected. As to the instruments used, UV-VIS spectra were obtained on a Hewlett-Packard "Lambda 2," the NMR spectra were recorded on a Bruker WP 200 in $CDCl_3$ solutions, and MS measurements were carried out on a Hewlett-Packard 5995 A.

UV-VIS Spectra

A spectrum of a 0.1 M solution of acetylacetone and NaOH in DMF (3 ml, quartz glass, layer thickness 1 cm) was recorded. After this, 0.2 ml of a $5 \cdot 10^{-3}$M solution of 5,5-dithiobis(2-nitro-benzoic acid) in DMF was added and two cycles were measured (constant intensive absorption at $\lambda_{max} = 491$ nm). Then, 0.1 ml of CCl_4 was added, and eight measurements in automatic cycles of 30 seconds were made in the range between 360 and 600 nm.

Preparation of the Dithioacetals

General Procedure. 0.04 mole of an aryl-acetonitrile was deprotonated with 0.04 mole NaOEt in 60 ml DMF at 0°C under a nitrogen atmosphere until the base was dissolved. Subsequently, 0.04 mole of the disulfide was added, and, after stirring for 3 minutes at 0°C, 20 ml of CCl_4 was added dropwise. This mixture was stirred at the same temperature for 5 hours and then allowed to warm to room temperature. The solution was washed with water and extracted with CCl_4 (3 × 20 ml). The organic layer was dried over Na_2SO_4 and concentrated and the residue was recrystallized from EtOH.

Bis(phenylthio)phenylacetonitrile **1a**. Yield 8.1 g (60, 5%); mp 75–76°C; ^{13}C NMR δ: 58.7 (-C (CN)-), 117.0 (-CN), 127.2–136.7 (Ph); MS: 224 (100%, $[PhC(SPh)CN]^+$), 333 (0.05%, M^+). Calcd. for $C_{20}H_{15}NS_2$: C, 72.04; H, 4.53; N, 4.20; S, 19.23. Found: C, 71.84; H, 4.40; N, 4.24; S, 18.80.

Bis(4-chlorophenyl)phenylacetonitrile **1b**. Yield 10.5 g (65%); mp 106°C; ^{13}C NMR δ: 58.6 (-C (CN)-), 116.3 (-CN), 126.8–137.9 (aryl); MS: 258 (100%, $[PhC(SAr)CN]^+$), 401 (0,05%, M^+). Calcd. for $C_{20}H_{13}Cl_2NS_2$: C, 59.70; H, 3.26; Cl, 17.62; N, 3.48; S, 15.94. Found: C, 59.81; H, 3.27; Cl, 18.01; N, 3.20; S, 16.01.

Bis(tetramethylenedithiocarbamoyl) phenylacetonitrile **1c**. Yield 1.3 g (8%); mp 124°C; ^1H NMR δ: 1.92–2.23 (8 H, m, C–CH_2), 3.97 (8 H, t, N–CH_2), 7.46–7.91 (5 H, m, Ph); ^{13}C NMR δ: 24.1 + 26.4 (CH_2–CH_2N), 50.8 + 56.9 (CH_2–CH_2N), 116.6 (CN), 125.3–131.6 (Ph and -C(CN)-), 188.7 (CS).

Bis(phenylthio)-4-chlorophenylacetonitrile **2a**. Yield 5.3 g (36%); mp 68–69°C; MS: 258 (100%, $[ClC_6H_4C(SPh)CN]^+$), 367 (0.05, M^+). Calcd. for $C_{20}H_{14}ClNS_2$: C, 65.29; H, 3.84; Cl, 9.64; N, 3.81; S, 17.43. Found: C, 64.95; H, 3.74; Cl, 9.85; N, 3.74; S, 17.43.

Bis(4-chlorophenylthio)-4-chlorophenylacetonitrile **2b**. Yield 12.4 g (71%); mp 109°C; MS: 292 (100%, $[ClC_6H_4C(SAr)CN]^+$), 435 (0.05%, M^+). Calcd. for $C_{20}H_{12}Cl_3NS_2$: C, 55.00; H, 2.77; Cl, 24.35; N, 3.21; S, 14.68. Found: C, 54.96; H, 2.79; Cl, 24.34; N, 3.03; S, 14.60.

Bis(phenylthio)-1-naphthylacetonitrile **3a**. Yield 2.3 g (15%); light yellow oil; MS: 166 (100%, $[naphthylCHCN]^+$), 383 (0.05%, M^+). From this mixture, 1.9 g (17%) phenylthio-1-naphthylacetonitrile **3c** could also be isolated, mp 107–108°C; MS: 166 (100%, $[naphthylCHCN]^+$), 275 (5.4%, M^+); ^1H NMR δ: 5.56 (1 H, s, -CH-), 7.19–8.14 (12 H, m, aryl). Calcd. for $C_{13}H_{18}NS$: C, 78.51; H, 4.76; N, 5.09; S, 11.64. Found: C, 78.43; H, 4.78; N, 4.98; S, 11.66.

Bis(4-chlorophenylthio)-1-naphthylacetonitrile **3b**. Yield 7.2 g (40%); mp 149°C; MS: 166 (100%, $[naphthylCHCN]^+$), 452 (0.5%, M^+). Calcd. for $C_{24}H_{15}Cl_2NS_2$: C, 63.72; H, 3.34; Cl, 15.67; N, 3.10; S, 14.17. Found: C, 63.55, H, 3.43; Cl, 15.94; N, 3.05; S, 13.72.

0.04 mol phenylacetonitrile, 0.04 mol NaOEt, and 0.02 mol diphenyl disulfide were reacted according to the description above giving a mixture of 2.2 g (33%) **1a** and 1.9 g (41%) diphenylfumaric dinitrile, mp 158–160°C (160–161°C [16]); MS: 230 (100%, M^+).

Reaction of Fluorene with Diaryl Disulfides

Typical Procedure. A mixture of 0.04 mol fluorene, 0.04 mol NaOEt, and 0.04 mol bis(4-chlorophenyl) disulfide was dissolved in 60 ml DMF at 0°C, and 20 ml of CCl_4 was added and stirred for 5 hours at this temperature. After having been allowed to warm to room temperature, the mixture was washed with water, extracted with CCl_4, dried over Na_2SO_4, and concentrated. The residue was recrystallised from EtOH.

9,9-Bis(4-chlorophenylthio)fluorene **5a**. Yield 7.0 g (39%); mp 147°C; MS: 307 (100%, $[9\text{-}(Cl\text{-}C_6H_4S)fluorene]^+$), 451 (3.4%, M^+). Calcd. for $C_{25}H_{16}Cl_2S_2$: C, 66.52; H, 3.57; Cl, 15.71; S, 14.20. Found: C, 66.39; H, 3.54; Cl, 15.55; S, 14.13.

9,9-Bis(4-chlorophenylthio)-2-nitrofluorene **5b**. Yield 2.4 g (12%); mp 162–163°C. Calcd. for $C_{25}H_{15}Cl_2NO_2S_2$: C, 60.49; H, 3.05; Cl, 14.28; N, 2.82; S, 12.92. Found: C, 60.46; H, 2.99; Cl, 14.20; N, 2.86; S, 12.46. From this mixture also 3.6 g dinitro-9,9′-bifluorenylidene **5e** was isolated, MS: (100%, M^+); mp > 300°C (388–390°C, mixture of 2,2′- and 2,7′-dinitro-9,9′-bifluorenylidene [17]). The reaction of diphenyl disulfide and fluorene under conditions described before gave a mixture of 1.7 g (19%) unreacted Ph_2S_2 and 5.9 g of a light yellow oil consisting of a mixture of 9,9-bis(phenylthio)fluorene **5c** and 9,9′-diphenylthio-9,9′-bifluorene **5d**. The data for **5c** are: MS: 109 (100%, SPh^+), 273 (47%, $[9\text{-}PhS\text{-}fluorene]^+$), 382 (0.1%, M^+), retention time 3.2 minutes; ^{13}C NMR δ: 66.6 (C-9), 5d: MS: 109 (100%, SPh^+), 546 (2,5%, M^+), retention time 7.1 minutes; ^{13}C NMR δ: 36.8 (C-9).

The reaction of diphenyl disulfide and 2-nitrofluorene under conditions described above yields 6.6 g (76%) unreacted diphenyl disulfide and 7.5 g (89%) dinitro-9,9′-bifluorenylidene **5e**.

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