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Three sulfur atom insertion into the S–S bond—pentasulfide preparation

Yihua Hou,[a] Imad A. Abu-Yousef[b] and David N. Harpp[a,*]

[a]Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6
[b]Department of Chemistry, American University of Sharjah, PO Box 26666, Sharjah, United Arab Emirates

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Abstract

Chloro(triphenylmethyl)trisulfide (**1**) reacts under mild conditions with symmetric primary dialkyl disulfides and aromatic disulfides giving pentasulfides as the main products in good yield and selectivity. A mechanism involving a triphenylmethyl alkyl/phenyl tetrasulfide intermediate is discussed. © 2000 Elsevier Science Ltd. All rights reserved.

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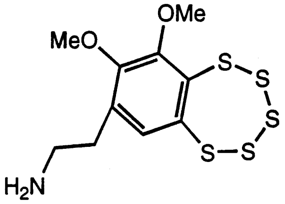
Pentasulfides occur in nature in a variety of plants and animals.[1] Two pentasulfides, diallylpentasulfide[2] and Varacin,[3] possess significant antitumor, antifungal and cytotoxic properties. Pentasulfides are also used as antifouling agents[4] and as components of lithium batteries.[5]



Varacin

Pentasulfides can be synthesized from the reaction of mercaptans or mercaptide salts with sulfur halides,[6] by nucleophilic displacement on sulfur[6] or the reaction of methoxycarbonyl trisulfanes with hydrogen sulfide.[7] However, these methods employ reagents that are difficult to handle or result in the formation of complicated polysulfide mixtures. As a continuation of our study of the reaction of thiosulfenyl chlorides with disulfides,[8] we have discovered that the reaction of chloro(triphenylmethyl)trisulfide (**1**) and disulfides **2** (Scheme 1) selectively affords pentasulfides **3** as the major product in good yield. This reaction can serve as an effective method to synthesize this difficult class from the more widely available disulfides.

$$\underset{\mathbf{1}}{Ph_3CSSSCl} + \underset{\mathbf{2}}{RSSR} \longrightarrow \underset{\mathbf{3}}{RSSSSSR} + \underset{\mathbf{4}}{Ph_3CCl}$$

Scheme 1.

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[*] Corresponding author.

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Dithiosulfenyl chloride **1** is a yellow solid prepared from triphenylmethanethiol and sulfur monochloride;[9] it is stable in the dark at −15°C for months. Its thermal stability[9] and reactions with olefins and dienes[10] have been reported.

The reaction of chloro(triphenylmethyl)trisulfide (**1**) and a solution of dimethyl disulfide (**2a**) in either CH_2Cl_2, $CHCl_3$, or benzene result in the formation of dimethylpentasulfide (**3a**) as the main product (Table 1). Dimethyltri-, tetra-, and hexasulfide were obtained as minor products.[11] In order to inhibit the further reaction of other reaction products with reagent **1**, only one equivalent of **1** is used. This reaction provides a model system to study the influence of solution concentration, the rate of addition, temperature and solvent.

Table 1
Three sulfur unit insertion into symmetric disulfides

Entry	R	Sulfide	Time (h)	Product	Selectivity (%)[a]	Yield (%)[b]
1	CH_3	**2a**	2	**3a**	86	67
2	CH_3CH_2	**2b**	2	**3b**	83	73
3	$PhCH_2$	**2c**	9	**3c**	90	74
4	$HOCH_2CH_2$	**2d**	2	**3d**	87	67
5	$CH_2{=}CHCH_2$[c]	**2e**				
6	4-NH_2Ph[d]	**2f**				
7	4-CH_3OPh	**2g**	2	**3g**	71	68
8	4-CH_3Ph	**2h**	48	**3h**	60	44
9	4-NO_2Ph[e]	**2i**				
10	*i*-Propyl	**2j**	12	**3j**[f]	86	74
11	*t*-Butyl	**2k**	12	**3k**[g]		

[a] The percentage of pentasulfides in all polysulfides formed as calculated from the integration of appropriate peaks in the ^{1}H NMR spectra.

[b] Calculated according to peak integration of the crude reaction mixture that includes some starting material and intermediate **7**.

[c] Reacted with the double bond.

[d] Dramatic reaction with the NH_2 group.

[e] 90% of starting disulfide remained after one week.

[f] Underwent disproportionation on the column.

[g] Negligible yield.

Solvent polarity is the strongest factor influencing the reaction in that the addition of polar solvents such as acetic acid or traces of water provide a significant increase in the rate. The selectivity of the reaction is linked with reaction temperature and solvent. The best procedure appears to be the following. Dimethyldisulfide (**2a**) (0.5 mmol, 47 mg) and **1** (0.5 mmol, 187 mg) were each dissolved in 5 mL of CH_2Cl_2. The solution of **2a** was quickly added to the solution of **1** and the reaction vessel capped. The reaction mixture was stirred at room temperature until the composition of the reaction mixture remained constant. The solvent was then evaporated under reduced pressure and the residue was passed through a silica gel (neutral, 230∼400 mesh) column, using hexane/ethyl acetate as the eluent. The more polar component, triphenylmethyl chloride (**4**) hydrolyzed to triphenylmethyl alcohol (**5**) on the column and was separated cleanly.

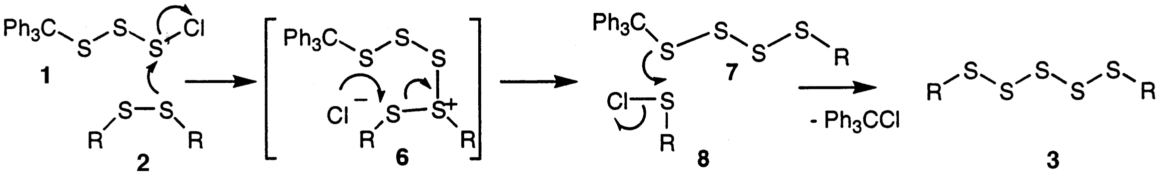
However, the complete separation of the main product from the side products by silica gel column appears impossible. In the case of dibenzyldisulfide (**2c**), pure pentasulfide product was obtained by repeated recrystallization.

A strong electronic effect was observed with a series of aryl disulfides with different substituents at the *para* position (entries 7–9). Electron-donating groups were found to accelerate the reaction and improve the yield of pentasulfide product while electron-withdrawing substituents (NO_2) kept disulfide **2i** essentially inert to the sulfur transfer reagent **1**.

To explore the limitations of the sulfur-transfer reagent **1**, substrates with different functional groups were examined (entries 4–6). It was discovered that the presence of the OH group in **2d** does not compete with the S–S bond to react with **1**, but accelerates the reaction. Reagent **1** reacted with the NH_2 group in **2f** in a dramatic fashion but the product(s) have not yet been identified. When **2e** was treated with **1**, analysis by ^1H NMR indicated the reaction of **1** with the double bond took priority over its reaction with the disulfide.

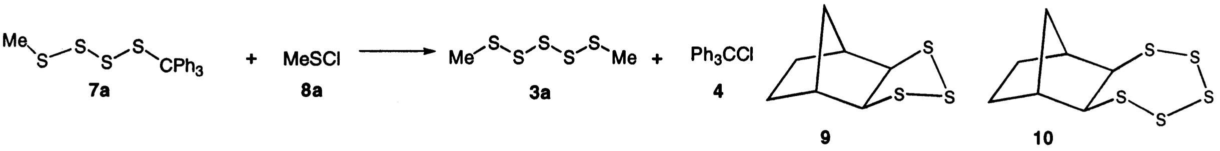
Secondary and tertiary disulfides react more slowly than primary or aromatic disulfides. Three equivalents of reagent **1** were required to completely react with diisopropyl disulfide (**2j**). The pentasulfide **3j** that formed underwent rapid disproportionation on a silica gel column. The reaction of **1** with *t*-butyl disulfide (**2k**) provided *t*-butyl pentasulfide (**3k**) only as a minor product even when excess **1** is used in the reaction mixture.

A free radical mechanism can be ruled out due to the strong correlation of reaction rate with the polarity of the solvent. In addition, adding a radical scavenger to the model reaction did not alter the rate or outcome of the product mixture. The first step of the reaction is believed to be a nucleophilic cleavage of the S–Cl bond by the disulfide.[8] This is similar to the reaction of arenesulfenyl chlorides with organic disulfides studied by Moore[12] and Pietra.[13] When this attack takes place with the relatively electron-rich sulfur atom in disulfide **2** engaging the electron-deficient sulfur in chloro(triphenylmethyl)trisulfide (**1**), a sulfonium salt **6** is formed as an intermediate and eventually triphenylmethylalkyl/phenyltetrasulfide (**7**) and sulfenyl chloride **8** are generated. The subsequent attack of the sulfur atom adjacent to the triphenylmethyl group in intermediate **7** on the sulfenyl chloride **8** leads to the formation of final product, pentasulfide **9** (Scheme 2). This mechanism is consistent with the electronic effect displayed by the reaction and the difficulty to induce the same reaction with secondary and tertiary disulfides.



Scheme 2.

There is considerable evidence to support this mechanism. When the reaction of **1** and dimethyldisulfide (**2a**) was followed by ^1H NMR in $CDCl_3$, the appearance and the disappearance of peaks relevant to intermediate **7a** (R = Me) and the sulfenyl chloride **8a** (R = Me) were observed. It was also noted that when this reaction was performed in anhydrous benzene, the formation of **7a** and **8a** proceeded much faster than their further reaction with each other. Thus, at a certain stage of the reaction (ca. 10–12 h), volatile **8a** can be evaporated with the solvent and **7a** left behind. Intermediate **7a** was purified by silica gel chromatography followed by recrystallization. Its structure was confirmed by NMR and MS.[14] More convincingly, when pure **7a** was treated with methanesulfenyl chloride (**8a**), prepared from dimethyl disulfide and sulfuryl chloride at −15°C, dimethylpentasulfide (**3a**) was obtained in good yield. In the reaction of cyclic trisulfide **9** with **1**, only two of the three sulfur atoms were ultimately delivered resulting in the known pentasulfide **10**[15] in 30% yield (Scheme 3). This apparently reflects the overall stability of the pentasulfide versus the hexasulfide. We are investigating these effects.



Scheme 3.

Clearly, the reaction of chloro(triphenylmethyl)trisulfide (**1**) with primary dialkyl disulfides and aromatic disulfides provides a practical new route to synthesize their pentasulfide homologs. We are continuing our study of this unusual transformation.

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