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Sulfur-atom insertion into the S–S bond—formation of symmetric trisulfides

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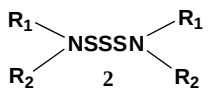
Abstract—The reaction of triphenylmethanesulfenyl chloride (**3a**) with acyclic disulfides **4** or **5** give the respective trisulfides **1** or **2** in moderate to good yield and selectivity. A mechanism is advanced to explain the chemistry.

Symmetric trisulfides have been found in many natural sources such as onions and garlic,[1] brown algae[2] and various animals.[3] Many of these trisulfides have significant biological importance.[4] A recent example is bis(2-hydroxyethyl)trisulfide **1d**.[5] It was separated from *Bacillus stearothermophilus* UK563 and shows cytotoxic, antitumor and immunostimulant activity. Another type of trisulfide, diamino trisulfides **2**, can be used as crosslinking and accelerating agents in polymerization reactions in the rubber industry as well as in pesticides.[6]

$$HOCH_2CH_2SSSCH_2CH_2OH$$

1d



2

Symmetrical trisulfides have been prepared by the reaction of sulfur dichloride with thiols[7] wherein olefinic or hydroxylic functions cause side reactions. Trisulfides are usually obtained as mixtures of polysulfides by the reaction of alkyl halides with sodium trisulfide,[8] thiols with sulfur,[9] the reaction of sodium or potassium sulfide with alkanesulfenyl chlorides[10] and other methods involving thiosulfonates.[11]

A practical method for the synthesis of diamino trisulfides was reported by Katritzky employing the reaction of diamino disulfides with sulfuryl chloride, sodium sulfide nonahydrate and sodium hydroxide.[6] The method is applicable to bis(*N*,*N*-dialkylamino)disulfides or bis(*N*,*N*-diallylamino)disulfides with yields of the trisulfides ranging from 47 to 81%. However, *N*-aryl substituted aminodisulfides give poor results because of the reaction of the aromatic rings with sulfuryl chloride.

As a continuation of our earlier studies on the reactions of chloro(triphenylmethyl)di- and trisulfide (**3b** and **3c**) with symmetrical disulfides,[12] we have discovered that the reaction of triphenylmethanesulfenyl chloride **3a** with acyclic symmetric disulfides **4** or **5** give the respective trisulfides in moderate to good yield and selectivity. This reaction serves as an alternative method of preparation of trisulfides using easily accessible disulfides.

Chloro(triphenylmethyl)sulfide (**3a**) is commercially available[13a] and can also be readily synthesized by the reaction of sulfuryl chloride with triphenylmethane thiol in ether[13b] followed by recrystallization from chloroform and ethanol at room temperature; reagent **3a** is stable in the freezer for years. It was also observed that heating it in chloroform solution caused its decomposition. Its addition reactions with thiiranes and olefins have been studied.[14]

The conditions of the reaction of **1a** with dimethyl disulfide were optimized by temperature, rate of addition, solvent and concentration of the reagents (Scheme 1). Quick addition of **1a** at room temperature to the solution of disulfide turned out to be the most favorable for the reaction. Much better yields and selectivity

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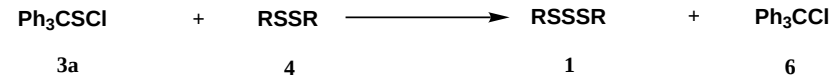


Scheme 1.

were obtained in methylene chloride, chloroform or benzene than in diethyl ether, THF or ethyl acetate. The rate of the reaction is much faster in polar solvents than in non-polar media; the reaction went to completion in about 2 h in chloroform while in benzene the reaction time was about 24 h. The reaction appears to be sensitive to traces of water or acid in benzene. It was observed that the reaction did not take place at all in well-dried benzene in 24 h, while in the same period of time, the reaction reached completion in analytical grade benzene. In the more polar chloroform, adding a drop of water or acetic acid has much less influence on the outcome of the reaction. By increasing the concentration of reagents from 0.1 to 0.2 mmol/mL in chloroform, the reaction time was decreased while yield and selectivity were improved moderately (5–10%).

The ratio of the two reagents has an essential influence on the selectivity of the reaction. Using a 1:1 ratio of **2** or **5** with **1a**, the only minor product is tetrasulfide. Using more than 1 equiv. of **1a** generally resulted in the formation of some higher polysulfides (Scheme 2).

The general synthetic procedure for the reaction is as follows: 1 mmol of disulfide was dissolved in 2 mL of chloroform and 1 mmol of **1a** in 3 mL of chloroform. The second solution was added into the first one and the flask capped. The mixture was stirred until **1a** was fully consumed (monitored by ^{13}C NMR). Water (5 mL) was added at the end of the reaction and the mixture stirred for 1 h. During this time, **4** was converted into triphenylmethanol, which in most cases is easily separated from the polysulfides by passing the mixture through a plug of silica gel and flashing with hexane or a mixture of hexane and ethyl acetate. It is more difficult to fully separate the trisulfides from the starting disulfides and side product tetrasulfides. Compound **3a** and **3b** can be purified by distillation under high vacuum[10] whereas **3c** was recrystallized from ethanol and **3e** from a mixture of benzene and hexane. Pure **3d** was obtained in 42% yield by careful chromatography on a silica gel column. Compound **3g** was purified by repeated column chromatography and recrystallization from hexane.

The reaction does show limitations. An amino group or olefin in substrates competed significantly with the S–S bond and reacted with the sulfur transfer reagent. On the other hand, the amide linkage or Cbz-protected amino group (entry 5, Table 1) did not react with **1a**. The OH group in substrates did not appear to interfere with the sulfur insertion; however, it was observed that **4** reacted with the OH group in the substrates or ethanol in commercial chloroform when the reaction mixture was stirred for 8–10 h (Scheme 3). Electron-withdrawing functions in the R group decreased the reactivity of the substrate with the sulfur transfer reagent and increased the reaction time considerably. Carboxylic acid substitution at the β-carbon of the disulfides or a nitro group at the *para* position of the benzene ring in aromatic disulfides can actually keep the substrates inert to the sulfur transfer reagent **1a**. To explore the possibility of applying this methodology to the synthesis of unsymmetric trisulfides, benzylethyl disulfide was reacted with **3a**. A complex mixture was formed suggesting little synthetic value to this aspect of the chemistry.

The insertion reaction is effective with diamino disulfides as substrates. This preparation of trisulfide **2** is simpler and proceeds under milder conditions compared with the reported method.[6] It was observed that

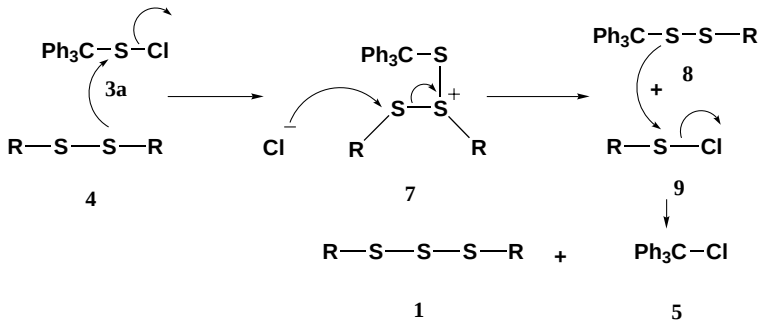
Scheme 2.

Table 1. One sulfur unit insertion into symmetric disulfides

Entry	R	Disulfide	Time (h)	Product	Yield (%)[a]	Selectivity (%)[b]
1	CH_3	**4a**	2	**1a**[15]	88	95
2	Et	**4b**	18	**1b**[11]	80	95
3	$PhCH_2$	**4c**	24	**1c**[16]	56	87
4	$HOCH_2CH_2$	**4d**	48	**1d**[4]	42	80
5	$CbzNHCH_2CH_2$	**4e**[17]	72	**1e**[18]	55	75
6	4-CH_3OPh	**4g**	48	**1g**[19]	52	77

[a] Isolated yield.

[b] Selectivity refers to the molar percentage of trisulfides in the mixture of trisulfides and tetrasulfides obtained from the reaction. The value was calculated from peak area ratios in the ^1H NMR spectra of the crude reaction mixtures.



Scheme 3.

Table 2. One sulfur unit insertion into symmetric diamino disulfides

Entry	5	Time (h)	6	Yield (%)
1	Dimorpholinodisulfide[20] (**5a**)	24	Dimorpholinotrisulfide[21] (**2a**)	75
2	Bis(*N*-benzyl-*N*-methyl)disulfide[22] (**5b**)	16	Bis(*N*-benzyl-*N*-methyl)trisulfide[22] (**2b**)	85
3	Bis(*N*,*N*-diethyl)disulfide[23] (**5c**)	24	Bis(*N*,*N*-diethyl)trisulfide[24] (**2c**)	80

under these conditions a reaction took place between **6** and the ethanol in commercial chloroform. As a result, triphenylmethylethyl ether[25] was isolated in high yield. To simplify the reaction products, ethanol-free chloroform was used in these cases. In the three entries listed in Table 2, the trisulfides were formed in good yield; the tetrasulfide impurity was minor. The three trisulfides decomposed significantly on a silica gel column (neutral, 230–400 mesh). Alternatively, the mixture was dissolved in the minimum amount of hexane and the solution was cooled in a refrigerator (−15°C). Most of the triphenylmethanol precipitated as a white solid. Trisulfide **2b** was fully purified by a careful recrystallization from a mixture of hexane and ethyl acetate; **2a** and **2c** were not fully purified.

We propose that this reaction shares a parallel mechanism as the reactions between chlorodisulfide **3b**[12a] or chlorotrisulfide **3c**[12b] with acyclic disulfides. Reagent **3a** shows much less reactivity than the two other reagents; however, unlike the reaction with **3c**, intermediate **8** was never directly observed.

In conclusion, the current method provides a novel and convenient preparation of some acyclic symmetric trisulfides from easily accessible starting materials under very mild conditions.

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18. Purified by chromatography and recrystallization; mp 89–90°C; ^{1}H NMR: δ 2.98 (t, $J=5.7$, 4H), 3.55 (t, $J=6.0$, 4H), 5.08 (s, 4H), 5.85 (s, 2H), 7.32 (m, 10H); ^{13}CNMR: δ 38.33, 39.31, 66.77, 128.10, 128.46, 136.27, 156.27; MS (CI): m/z (%) 422 (1.84, M^+), 91 (100, $PhCH_2^+$); satisfactory elemental analysis for C, H, N, S was obtained.
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21. Yellow oil; ^{1}H NMR: δ 3.05 (t, $J=4.8$, 8H), 3.73 (t, $J=4.8$, 8H); ^{13}CNMR: δ 55.67, 66.81; MS (EI): m/z (%) 268 (2.65, M^+), 236 (2.59, $M-S^+$), 204 (4.24, $M-S_2^+$), 85 (72.27), 86 (35.46), 87 (73.99); HRMS (EI): m/z calculated, 268.0374; found, 268.0380.
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24. Yellow oil; ^{1}H NMR: δ 1.21 (t, $J=7.2$, 12H), 3.00 (q, $J=7.2$, 8H); ^{13}CNMR: δ 13.15, 51.69; MS (FAB): m/z (%) 240 (17.17, M^+), 208 (17.72, $M-S^+$), 176 (19.58, $M-S_2^+$); HRMS (EI): m/z calcd, 240.0789; found, 240.0793
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