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TBAF Promoted Formation of Symmetrical Trisulfides

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ABSTRACT: *We have developed a new method for the synthesis of functionalized symmetrical trisulfides based on (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorin-2-yl)disulfanyl derivatives prepared from readily available 5,5-dimethyl-2-sul-fanyl-2-thioxo-1,3,2-dioxaphosphorinane or bis(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) disulfide. The symmetrical trisulfides can be obtained from aliphatic and aromatic thiols and* L*-cysteine derivatives under mild conditions with high yield and purity*. © 2013 Wiley Periodicals, Inc. Heteroatom Chem. 25:10–14, 2014; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21129

INTRODUCTION

The biological importance of the sulfur–sulfur bond also comprises organic trisulfides. Trisulfide functionality was observed in the compounds isolated from plants in the onion family [1] (genus *Allium*), proteins [2], in the tumor inhibitors calicheamicin [3], esperamicin [4], members of the enediyne group of antibiotics. From this point of view, the trisulfide functionality has been recognized as an important target in organic synthesis. Preparation of symmetrical, acyclic trisulfides without additional functional groups is very well documented [5]. Most common methods for their preparation are based on reaction of thiols with sulfur [6], sulfur dichloride [7], or coupling of alkyl halides with sodium trisulfide [8]. Most suitable substrates used in the synthesis of trisulfides include Bunte salts [9], metal sulfides [10], and thiosulfenyl chloride [11]; the latter can also be used for the preparation of unsymmetrical trisulfides. Other practical procedures involve the reduction of thiosulfonates and disulfonyl sulfides with phosphines [12], sulfur insertion reactions into thiosulfinates, thiosulfonates [13], and disulfides [14], alkoxide decomposition of sulfenyl thiocarbonates [15], and reactions of thiols with 1,1′-thiobis(benzimidazole) [16] or bis(imidazolyl) sulfide [17].

Although the synthesis of symmetrical trisulfides is well documented, their preparation is in fact more complicated. Most of the abovementioned methods suffer either from moderate yields or formation of undesired polysulfide side products. The most convenient removal of these impurities can be accomplished by crystallization. However, it can be applied only to solid trisulfides. Other methods may require multistep synthesis of appropriate precursors or using freshly distilled sulfur dichloride. Very often, the presence of additional functional groups, especially unprotected, limits the scope of these methods.

We have previously demonstrated the preparation of functionalized unsymmetrical compounds, such as dialkyl disulfides, alkyl aryl disulfides [18], diaryl disulfides [19], "bioresistant" disulfides [20], and unsymmetrical disulfides based on L-cysteine and L-cystine derivatives [21]. We were also able to obtain functionalized symmetrical [22] and unsymmetrical [23] trisulfides bearing alkyl, aryl groups and L-cysteine derivatives based on

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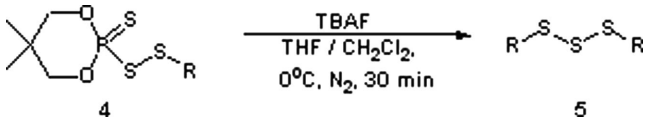


SCHEME 1 Preparation of symmetrical trisulfides **5**.

TABLE 1 Preparation of Symmetrical Trisulfides **5**

Entry	*R*	*5*	*Yield (%)*
1	$-(CH_2)_{11}CH_3$	**5a**	94
2	$-(CH_2)_{11}OH$	**5b**	97
3	$-(CH_2)_{10}COOH$	**5c**	92
4	$-(CH_2)_2OH$	**5d**	91
5	$-(R)$-$CH_2CH(NHBoc)CO_2Et$	**5e**	85
6	-4-C_6H_4-CH_3	**5f**	87

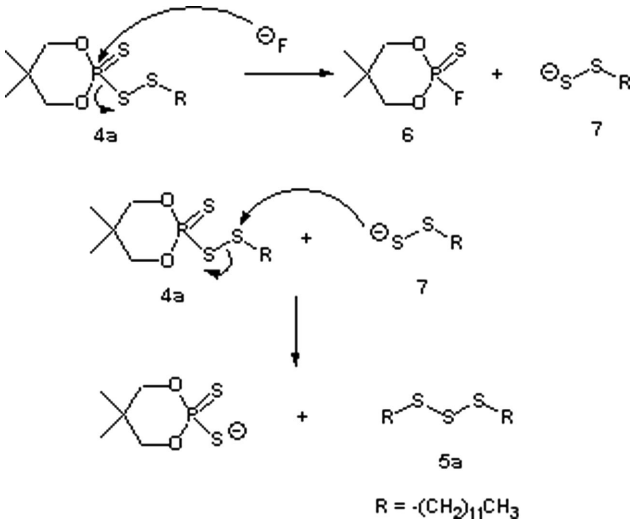
the phosphorodithioic acid derivatives. These excellent results encouraged us to extend the strategy to the preparation of symmetrical trisulfides based on readily available (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl derivatives **4**. Compounds **4** can be obtained from either phosphorodithioic acid **1** or its disulfide **2** by treatment with bromine to quantitatively afford sulfenyl bromide **3**, which subsequently, without isolation, reacts with thiols [22].

The purification of starting material, phosphorodithioic acid **1**, has been previously accomplished by vacuum distillation [24]. The vacuum must be kept below 1.5 mmHg upon heating; otherwise content of the flask can decompose and sometimes explode. We have found that crude phosphorodithioic acid **1** can also be purified by crystallization from carbon tetrachloride with 60% yield. Moreover, filtrate after crystallization can be used for the preparation of ammonium salt required for synthesis [20] of phosphorodithioic acid disulfide **2**. The modified procedures (see *Experimental*) for the preparation of phosphorodithioic acid **1** and its disulfide **2** make the developed method of symmetrical trisulfide synthesis more common and versatile.

RESULTS AND DISCUSSION

We report here an extension of our previously reported procedure [22] for the synthesis of symmetrical trisulfides. Treatment of 1.0 equivalent of 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl derivative **4** with 1.05 equivalent of tetra *n*-butylammonium fluoride (TBAF) in the mixture of THF and CH_2Cl_2 afforded symmetrical trisulfides **5** (Scheme 1, Table 1).

Although the yields are very high, much more important is the exclusive formation of the trisulfide without the formation of undesired polysulfide side



SCHEME 2 Proposed mechanism for the formation of trisulfide **5a**.

products. The formation of the trisulfide product can be explained by the nucleophilic attack of the fluoride anion from TBAF on the phosphorus atom of the disulfanyl derivative **4a**. The driving force in this step seems to be the high affinity of fluoride to phosphorus (bond dissociation energy for the P–F bond = 439 kJ/mol) [25]. This leads to the formation of a phosphorothioic acid fluoride **6** and dodecyldisulfide anion **7.** In the next step, anion **7** reacts with still present in the reaction mixture disulfanyl derivative **4a** to produce the symmetrical didodecyl trisulfide **5a** (Scheme 2).

As can be seen from the proposed mechanism, the reaction should also be accomplished with 0.5 equivalent of TBAF. Unfortunately, in this case, the reaction was very sluggish and the product was contaminated with symmetrical di- and tetrasulfide. It looks like the first step of the reaction of fluoride ion at the phosphorus atom is the slowest. Moreover, disulfide anion **7** should be consumed very quickly, so the sulfur extrusion can be avoided and formation of corresponding symmetrical disulfide may be excluded. The increased rate of the first step of reaction and higher concentration of disulfide anion **7** (in this case, this anion is also consumed faster in the reaction with derivative **4**) can be achieved by using excess of TBAF. Although di-, tri-, and tetrasulfides cannot be separated by column chromatography, the presence of these impurities can be easily confirmed by ^1H nuclear magnetic resonance (NMR). The chemical shift of the methylene group (triplet in $CDCl_3$) connected with sulfur for di-, tri-, and tetrasulfide is 2.66, 2.87, and 3.05, respectively. When the ^{31}P NMR spectrum of reaction mixture was recorded then the presence of phosphorothioic

acid fluoride **6** (52.1 ppm) and phosphorodithioic acid **1** anion (110.1 ppm) was observed what supports proposed mechanism. We have also noticed that the formation of trisulfide is effected by steric hindrance. When disulfanyl derivatives **4** (R = *tert*-butyl or triphenylmethyl) were treated with TBAF, then trisulfides were not formed and starting materials were recovered with 85% and 90% yield, respectively. It seems that the attack of fluoride ion at the phosphorus atom of compound **4** is very slow and the subsequent reaction of generated disulfide anion with these compounds is suppressed by the steric congestion of the R group (R = *tert*-butyl or triphenylmethyl) (Scheme 2). We have also noticed that the developed method cannot be applied for the effective formation of unsymmetrical trisulfides. When the mixture of **4a** and **4b** (1:1 ratio) was treated with TBAF, the corresponding unsymmetrical trisulfide ($CH_3(CH_2)_{11}S_3(CH_2)_{11}OH$) [23] was isolated with 45% yield. The symmetrical trisulfide **5a** (40%) and **5b** (42%) were also isolated. However, the scope of that approach is strongly limited by the formation of symmetrical products and possibility of their separation from unsymmetrical trisulfide by column chromatography. The above limitations have encouraged us to develop a new synthetic strategy for the preparation of unsymmetrical trisulfides bearing the additional functionalities at both sides. These results will be reported in due course.

In conclusion, presented reactions took place under mild conditions without any additional catalysts or reagents, except for commercially available TBAF. The symmetrical trisulfides can be obtained from aliphatic and aromatic thiols and also L-cysteine derivatives. The presence of functional groups: amino, hydroxy, or carboxy did not disturb the course of the reaction. The advantages of this new method are the easily accessible starting materials, convenient manipulation, short reaction times, and very high purities and yields. From this point of view, the above-presented method for the synthesis of symmetrical trisulfides seems to be currently one of the most versatile and convenient approaches to preparation of functionalized symmetrical trisulfides.

EXPERIMENTAL

Tetrabutylammonium fluoride (1 M in THF) is commercially available from Sigma-Aldrich (Milwaukee, WI, USA). (5,5-Dimethyl-2-thioxo-1, 3, 2-dioxaphosphorinan-2-yl)disulfanyl derivatives **4a–f** [22] were synthesized by described procedures. Dichloromethane and toluene (POCh, Gliwice, Poland) were dried before use. Column chromatography was performed using silica gel 60 (230–400 mesh, Merck). Thin layer chromatography was performed with silica gel Polygram SIL G/UV254 (Macherey–Nagel, Düren, Germany). Melting points were measured with a Gallenkamp 7936B (Gallenkamp, Loughborough, England) apparatus and are uncorrected. NMR spectra were recorded on Varian Gemini 500 or 200 MHz (Palo Alto, CA, USA) spectrometers. The residual solvent peak was used as the internal reference (CDCl3: $\delta = 7.26$ ppm for ^{1}H, $\delta = 77.0$ ppm for ^{13}C). An external standard (85% H_3PO_4: $\delta = 0$ ppm) was used as the reference for recording the ^{31}P NMR spectra. Mass spectra of ESI (electrospray ionization) of positive ions were registered on an Agilent 6230 Accurate Mass TOF instrument (Agilent Technologies, Santa Clara, CA, USA).

5, 5-Dimethyl-2-sulfanyl-2-thioxo-1, 3, 2-dioxaphosphorinane **1**

To a suspension of P_4S_{10} (44.8 g, 0.1 mol) in dry toluene (260 mL), a 2,2-dimethylpropane-1,3-diol (41.6 g, 0.4 mol) was added [24]. The reaction mixture was stirred at 60–80°C for 15 h under nitrogen, then traces amount of unreacted P_4S_{10} were filtered off. Solvent was evaporated under reduced pressure and the residue was kept under vacuum at room temperature for 30 min. The obtained sticky solid was dissolved in hot CCl_4 (25 mL for each 10 g of crude product) and placed in the freezer (–15°C) for 6 h. Product was filtered off and dried under vacuum at room temperature to yield 47.6 g (0.24 mol, 60%); the residue from filtrate after evaporation of CCl_4 under reduced pressure can be used for the preparation of phosphorodithioic acid ammonium salt.

Melting point (mp) 81–82°C (Lit. [24c] 81–82°C), ^{31}P NMR ($CDCl_3$) = 77.68.

Bis-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanyl) disulfide **2**

A dry ammonia gas was passed through the solution of 5,5-dimethyl-2-sulfanyl-2-thioxo-1,3,2-dioxaphosphorinane **1** (47.6 g, 0.24 mol) [or the residue from filtrate after evaporation of CCl_4 (32 g, 0.16 mol)] in the mixture of toluene (350 mL) and diethyl ether (50 mL) (ether is required to produce precipitate that is easier to filtered off) cooled in an ice bath for 30 min [24]. White precipitate was filtered off and washed with toluene (50 mL) and ether (50 mL). After filtration, ammonium salt was dried under vacuum to yield 49.5 g (0.23 mol, 96%) (or 28 g 0.13 mol, 81% from the residue after evaporation

filtrate) of white powder; mp 263–265°C, (^{31}P NMR (D_2O) = 110.22).

A solution of the ammonium salt of phosphorodithioic acid (43 g, 0.2 mol) in water (300 mL) was stirred at room temperature and a solution of I_2 (25.4 g, 0.1 mol) and KI (50 g, 0.31 mol) in water (200 mL) was dropwise added. The brown solid was filtered off, washed with water (400 mL), and dissolved in ethyl acetate (1 L). Solution was washed with 10% $Na_2S_2O_3$ aqueous solution (150 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was recrystallized from ethanol to yield disulfide **2** (33.5 g 0.085 mol, 85 %); mp 133–134°C (Lit. [24c] 133.5–134°C), ^{31}P NMR ($CDCl_3$) = 80.87.

Trisulfides **5a–f** *(Typical Procedure)*

A solution of TBAF (0.274 g, 1.05 mmol) in THF (10 mL) was added to the solution of **4** (1.0 mmol) in dry CH_2Cl_2 (10 mL) at 0°C under N_2 atmosphere. The mixture was stirred for 30 min and then evaporated under reduced pressure. The residue was purified by column chromatography.

*Didodecyl Trisulfide (***5a***)*

Melting point 15–16°C (Lit.[22] 15–16°C), R_f = 0.3 (petroleum ether), waxy white solid; yield: 94% (204 mg, 0.47 mmol).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.5 Hz, 6H, CH_3), 1.15–1.45 (m, 36H, CH_2), 1.64–1.84 (m, 4H, CH_2), and 2.88 (t, J = 7.3 Hz, 4H, SCH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.9, 31.9, 29.6, 29.6, 29.5, 39.3,29.2, 28.8, 28.5, 22.7, and 14.1. Signals: expected, 12; observed, 11.

High-resolution mass spectrometry (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{51}S_3$: 435.3153; found: 435.3155.

*Bis(11-hydroxyundecyl) Trisulfide (***5b***)*

Melting point 61–63°C (Lit.[22] 61–63°C), R_f = 0.35 ($CHCl_3$–MeOH, 25:1), white solid; yield: 97% (213 mg, 0.49 mmol).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20–1.46 (m, 28H, CH_2), 1.39 (s, 2H, OH), 1.46–1.65 (m, 4H, CH_2), 1.65–1.82 (m, 4H, CH_2), 2.87 (t, J = 7.3 Hz, 4H, SCH_2), and 3.64 (t, J = 6.5 Hz, 4H, OCH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 63.0, 38.8, 32.7, 29.5, 29.4, 29.1,28.8, 28.5, and 25.7. Signals: expected, 11; observed, 9.

High-resolution mass spectrometry (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{46}NaO_2S_3$: 461.2558; found: 461.2561.

*Bis(10-carboxydecyl) Trisulfide (***5c***)*

Melting point 79–81°C (Lit.[22] 79–81°C), R_f = 0.3 ($CHCl_3$–MeOH, 25:1), white solid; yield: 92% (215 mg, 0.46 mmol).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24–1.50 (m, 24H, CH_2), 1.54–1.84 (m, 8H, CH_2), 2.36 (t, J = 7.3 Hz, 4H, CH_2COO), 2.88 (t, J = 7.3 Hz, 4H, SCH_2), and 8.90 (br s, 2H, COOH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 180.2, 38.8, 34.0, 29.3, 29.3, 29.1,29.1, 29.0, 28.8, 28.4, and 24.6. Signals: expected, 11; observed, 11.

High-resolution mass spectrometry (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{42}NaO_4S_3$: 489.2143; found: 489.2149.

*Bis(2-hydroxyethyl) Trisulfide (***5d***)*

R_f = 0.25 ($CHCl_3$–MeOH, 25:1), colorless oil; yield: 91% (85 mg, 0.46 mmol)[16,26].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.16 (s, 2H, OH), 3.09 (t, J = 5.7 Hz, 4H, SCH_2), 3.99 (t, J = 5.7 Hz, 4H, OCH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 59.5, 41.7. Signals: expected, 2;observed, 2.

High-resolution mass spectrometry (ESI): m/z $[M + Na]^+$ calcd for $C_4H_{10}NaO_2S_3$: 208.9741; found: 208.9746.

*Bis[(R)-2-(tert-butoxycarbonylamino)-2-(ethoxycarbonyl)ethyl] Trisulfide (***5e***)*

Melting point 74–77°C (Lit. [22] 74–77°C), R_f = 0.32 (CH_2Cl_2–EtOAc, 25:1), white solid; yield: 85% (225 mg, 0.43 mmol).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 6H, $COOCH_2CH_3$), 1.46 (s, 18H, Boc), 3.37 (d, J = 4.8 Hz, 4H, SCH_2), 4.23 (q, J = 7.1 Hz, 4H, $COOCH_2$), 4.56–4.72 (m, 2H, CH), and 5.44(d, J = 7.8 Hz, 2H, BocNH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.3, 155.0, 80.2, 61.9, 52.9,41.1, 28.3, and 14.1. Signals: expected, 8; observed, 8.

High-resolution mass spectrometry (ESI): m/z $[M + Na]^+$ calcd for $C_{20}H_{36}N_2NaO_8S_3$: 551.1531; found: 551.1536.

*Bis(4-tolyl) Trisulfide (***5f***)*

Melting point 76–77°C (Lit. [[7]a] 78–79°C), R_f = 0.35 (CH_2Cl_2–petroleum ether, 1:2), bright yellow solid; yield: 87% (121 mg, 0.44 mmol).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.36 (s, 6H, CH_3), 7.12 (d, J = 7.9 Hz, 4H, Ar), and 7.45 (d, J = 7.9 Hz, 4H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.6, 131.0, 129.8, 128.5, and 21.2. Signals: expected, 5; observed, 5.

High-resolution mass spectrometry (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{14}NaS_3$: 301.0155; found: 301.0161.

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