Novel and Efficient Methods for the Synthesis of Symmetrical Trisulfides

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Abstract: We have developed convenient methods for the synthesis of symmetrical trisulfides under mild conditions in very good yields. The described methods are based on the straightforward preparation of (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorin-2-yl)disulfanyl derivatives from readily available 5,5-dimethyl-2-sulfanyl-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 also L-cysteine derivatives.

Key words: symmetrical trisulfides, thiols, sulfenyl bromides, L-cysteine

The biological importance of the sulfur–sulfur bond also includes organic trisulfides. Several trisulfides have been isolated from natural sources[1] especially from plants in the onion family (genus *Allium*). The trisulfide functionality was also found in the tumor inhibitors calicheamicin[2] and esperamicin,[3] members of the enediyne group of antibiotics. The preparation of symmetrical, acyclic trisulfides is well documented.[4] The most common methods for obtaining trisulfides include the reaction of thiols with sulfur dichloride,[5] the coupling of alkyl halides with sodium trisulfide,[6] the reaction of thiols or disulfides with sulfur.[7] Thioalkylation of various thiosulfenate species can also produce trisulfides. The most suitable substrates include Bunte salts,[8] metal sulfides,[9] and thiosulfenyl chloride;[10] the latter can be used for preparation of unsymmetrical trisulfides. Other practical procedures involve the reduction of thiosulfonates and disulfonyl sulfides with phosphines,[11] sulfur insertion reactions into thiosulfinates, thiosulfonates,[12] and disulfides,[13] alkoxide decomposition of sulfenyl thiocarbonates,[14] and reactions of thiols with 1,1′-thiobis(benzimidazole)[15] or bis(imidazolyl) sulfide.[16]

The preparation of unsymmetrical trisulfides is not usually trivial. There are known procedures based on the coupling of chloro disulfides with *N*-arylamidothiosulfites[17] or thiols,[18] the sequential coupling of two thiols using sulfur dichloride.[19] Other procedures involve the desulfurization of unsymmetrical dialkanesulfonic thioanhydrides,[11] or require the use of unstable, in most cases, hydrodisulfides.[20]

Although the preparation of symmetrical trisulfides is straightforward and well documented, the synthesis of these compounds is in fact more complex. Most of the above methods suffer from either moderate yields or the formation of undesirable polysulfide side products. The removal of these impurities is, in most cases, not possible. The best method of purification is crystallization, but it can only be applied to solid trisulfides. Other methods require the multistep synthesis of appropriate precursors or using freshly distilled sulfur dichloride.[5] Additionally, the presence of functional groups is very often compromised by the reagents used and conditions of the reaction.

We have previously demonstrated the preparation of functionalized unsymmetrical molecules, such as dialkyl disulfides, alkyl aryl disulfides,[21] 'bioresistant' disulfides,[22] unsymmetrical disulfides based on L-cysteine and L-cystine derivatives,[23] and diaryl disulfides.[24] 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.

Treatment of the stable and readily available bis(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) disulfide (**1**, Method A) or 5,5-dimethyl-2-sulfanyl-2-thioxo-1,3,2-dioxaphosphorinane (**2**, Method B) with bromine at –30 °C quantitatively affords 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-sulfenyl bromide (**3**) (Table 1).

Subsequent treatment, without prior isolation, of sulfenyl bromide **3** with a variety of thiols provides the corresponding (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl derivatives **4a–f**, which can be isolated in very good yields (Table 1, entries 1–6). These compounds are stable at room temperature for several months; decomposition by moisture or formation of symmetrical disulfides was not observed.

The reaction of disulfide **4a** with one equivalent of potassium *O*-*tert*-butyl dithiocarbonate was intended to prepare *O*-*tert*-butyl *S*-dodecylsulfanyl dithiocarbonate [$CH_3(CH_2)_{11}SSCSO$*t*-Bu], a convenient precursor of dodecyl hydrodisulfide. Surprisingly, when the above reagents were allowed to react in methanol at room temperature, both dodecyl tetra- and trisulfide were produced in a ratio of approximately 1:8. When the same reaction of **4a** was repeated with 1.1 equivalent of potassium *O*-*tert*-butyl dithiocarbonate in methanol at 0 °C until **4a** was consumed (TLC monitoring, ca. 30 min), then didodecyl trisulfide (**5a**) was isolated in 90% yield (Table 2, Method A, entry 1). The mechanism of the reaction may be formu-

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