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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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