Novel and Efficient Synthesis of Unsymmetrical Trisulfides

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Abstract: We have developed a convenient method for the synthesis of unsymmetrical trisulfides under mild conditions in very good yields. The designed method is based on the straightforward preparation of 1-[(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)trisulfanyl]dodecane from readily available 5,5-dimethyl-2-sulfanyl-2-thioxo-1,3,2-dioxaphosphorinane, sulfur dichloride (SCl_2) and dodecane-1-thiol. The unsymmetrical trisulfides can be obtained from aliphatic, aromatic thiols and L-cysteine derivatives as well.

Key words: unsymmetrical trisulfides, sulfur dichloride, thiols, L-cysteine, phosphorodithioic acid

Organic polysulfides have attracted significant interest during the past years, initially because of their interesting physical properties and potential for synthetic utility. More recently, several unprecedented classes of biologically active natural products containing polysulfide functionality have been discovered. Varacin the first naturally occurring compound determined to contain the 1,2,3,4,5-pentathiepin ring system, was isolated from a marine ascidian and exhibited significant antifungal and cytotoxic activities. It was as much as 100 times more potent than 5-fluorouracil toward the human colon cancer cell line HCT 116. The synthesis, reactivity, and biological activity of pentathiepins has been recently reviewed by Rakitin and Rees.[1] The trisulfide functionality is found in the tumor inhibitors calicheamicin[2] and esperamicin,[3] members of the enediyne group of antibiotics. The trisulfide functionality is also observed in lissoclinotoxin A.[4]

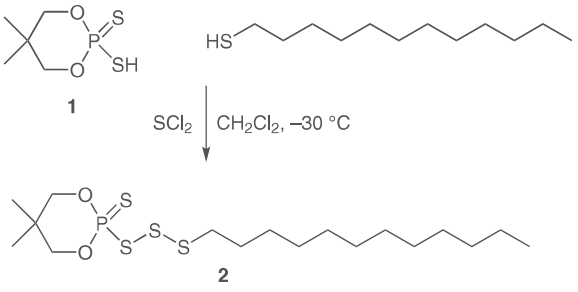
The most common methods for obtaining symmetrical trisulfides include the reaction of thiols with sulfur dichloride,[5] the coupling of alkyl halides with sodium trisulfide,[6] and the reaction of thiols or disulfides with sulfur.[7] Thioalkylation of various thiosulfenate species can also produce trisulfides. The most suitable substrates include Bunte salts,[8] metal sulfides,[9] and thiosulfenyl chloride.[10] The latter can also be used for preparation of unsymmetrical trisulfides. Other 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 sulfenylthiocarbonates,[14] and reactions of thiols with 1,1′-thiobis(benzimidazole)[15] or diimidazolylsulfide.[16]

Although the preparation of symmetrical, acyclic trisulfides is well documented,[17] the synthesis of unsymmetrical trisulfides is more complex. There are known procedures based on the coupling of chlorodisulfides with *N*-arylamidothiosulfites[18] or thiols[19,20] or the sequential coupling of two thiols using sulfur dichloride.[21] Other procedures involve the desulfurization of unsymmetrical dialkanesulfonic thioanhydrides,[11] or the use of (often) unstable hydrodisulfides.[22]

Most of the above methods suffer from either moderate yields or the formation of undesirable polysulfide side products. The removal of these impurities in most cases is not possible. The best method of purification is crystallization, but clearly this can only be applied to solid trisulfides. Other methods require the multistep synthesis of appropriate precursors or using freshly distilled sulfur dichloride.[5] Additionally, various functional groups are not compatible with the reagents and reaction conditions.

We have previously demonstrated the preparation functionalized unsymmetrical molecules, such as dialkyl disulfides, alkyl-aryl disulfides,[23] 'bioresistant' disulfides,[24] unsymmetrical disulfides based on L-cysteine and L-cystine derivatives,[25] and diaryl disulfides.[26] The excellent results encouraged us to extend the strategy to the preparation of symmetrical trisulfides based on the readily available 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives.[27]

We report a modification our latest extension of the strategy for preparation of unsymmetrical trisulfides. The treatment of a mixture of 5,5-dimethyl-2-sulfanyl-2-thioxo-1,3,2-dioxaphosphorinane (**1**)[28] and dodecane-1-thiol with sulfur dichloride SCl_2 at –30 °C afforded 1-[(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)-trisulfanyl]dodecane (**2**) in 68% yield after column chromatography (Scheme 1).



Scheme 1 The preparation of 1-[(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)trisulfanyl]dodecane (**2**)

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