Efficient Synthesis of Functionalized Unsymmetrical Dialkyl Trisulfanes

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Abstract: We have developed a convenient method for the synthesis of functionalized unsymmetrical dialkyl trisulfanes under mild conditions in very good yields. The designed method is based on the reaction of (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)-disulfanyl derivatives with alkyl disulfanyl anions generated in situ from *S*-acetyl disulfanyl derivatives and sodium methoxide. The developed method allows for the preparation of unsymmetrical trisulfanes bearing additional hydroxyl, carboxyl, or amino functionalities on both sides of the trisulfane functionality.

Key words: unsymmetrical trisulfanes, thiols, hydrodisulfanes, *S*-acetyl alkyldisulfanes, phosphorodithioic acid

Our interest in the chemistry of diorganyl trisulfanes (trisulfides) arises from their diverse roles in living organisms and their occurrence in natural sources.[1,2] In the literature, these compounds are often termed as organic trisulfides, but the IUPAC recommended nomenclature is trisulfanes.[3] The name trisulfide should only be applied to ionic compounds, such as Na_2S_3. Organic trisulfanes have been isolated from shiitake mushrooms,[4] oil made from *erula asafetida*,[5] durian fruit,[6] garlic oil,[7,8] and Hawaiian algae.[9] It also should be mentioned that dialanyltrisulfane has been detected in acidic wool hydrolysates, but it is not clear whether the related amino acid $(HOOCCH(NH_2)CH_2)S_3$ is a part of the wool structure or is formed from cysteine during hydrolysis.[10] In the biochemical literature, dialanyltrisulfane is often incorrectly termed as 'cysteine trisulfide'. A natural peptide containing a trisulfane group in place of a disulfane bridge has been isolated from genetically engineered *Escherichia coli* bacteria.[11] It is a derivative of the human growth hormone consisting of 191 amino acids in a single chain with a trisulfane bridge between cysteine (alanyl) residues 182 and 189.[12] A trisulfanyl functionality has also been observed in recombinant DNA-derived methionyl human growth hormone in the bridge between cysteine residues 53 and 165.[13] Calicheamicin[14,15] and esperamicins A_1 and A_2,[16,17] members of the enediyne class of antibiotics, also contain the trisulfanyl functionality. These natural products are very potent antitumor antibiotics.

There are numerous reactions that can be used to prepare symmetrical organic trisulfanes. The most common methods include the reaction of thiols with sulfur dichloride,[18] the coupling of alkyl halides with sodium trisulfide,[19] and the reaction of thiols or disulfanes with sulfur.[20] Thioalkylation reactions of various thiosulfenate species can also produce trisulfanes. The most suitable substrates include Bunte salts,[21] metal sulfides,[22] and thiosulfenyl chloride.[23] The latter can also be used for the preparation of unsymmetrical trisulfanes. Other practical procedures involve the reduction of thiosulfonates and disulfonyl sulfides with phosphines,[24] sulfur insertion reactions into thiosulfinates, thiosulfonates,[25] and disulfanes,[26] alkoxide decomposition of sulfenylthiocarbonates,[27] and reactions of thiols with 1,1-thiobis(benzimidazole)[28] or diimidazolylsulfide.[29]

Preparative methods that are efficient for the preparation of symmetrical trisulfanes are very often ineffective for the preparation of unsymmetrical compounds. Indeed, the synthesis of unsymmetrical trisulfanes is more complex. There are known procedures based on the coupling of chlorodisulfanes with *N*-arylamidothiosulfites[30] or thiols[31,32] or the sequential coupling of two thiols using sulfur dichloride.[33] Other procedures involve the desulfurization of unsymmetrical dialkanesulfonic thioanhydrides,[24] or the use of (often) unstable hydrodisulfanes.[34]

Moderate yields and/or the formation of undesirable polysulfane side products are the major drawbacks of the methods presented above. The likelihood that pure trisulfanes can be separated from the reaction mixture is very poor. The best purification method is crystallization, but clearly this can only be applied to solid products. Moreover, the scopes of the presented methods are limited by the availability of reagents and the chemical reactivity of the additional functional groups.

We have previously demonstrated the preparation of functionalized unsymmetrical molecules such as dialkyl disulfanes, alkyl-aryl disulfanes,[35] 'bioresistant' disulfanes,[36] unsymmetrical disulfanes of L-cysteine and L-cystine,[37] and diaryl disulfanes[38] based on the readily available 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives **1**. These disulfanyl derivatives **1** of phosphorodithioic acid were also convenient for the preparation of α-sulfenylated carbonyl compounds[39] and symmetrical trisulfanes.[40]

The limitations of our previous method for the preparation of unsymmetrical trisulfanes[41] have encouraged us to develop a new synthetic strategy for the preparation of unsymmetrical trisulfanes bearing additional functionalities on either side of the trisulfane. The idea is based on the reaction of electrophilic disulfanyl derivatives of phospho-

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