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An efficient and convenient synthesis of unsymmetrical disulfides from thioacetates

Slawomir Lach, Sebastian Demkowicz, Dariusz Witt *

Department of Organic Chemistry, Chemical Faculty, Gdansk University of Technology, Narutowicza 11/12, Gdansk 80-233, Poland

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ABSTRACT

We have developed convenient methods for the synthesis of functionalized unsymmetrical dialkyl disulfides 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 **1** with functionalized alkyl thiolate anions, generated in situ from thioacetates **2** and sodium methoxide or butylamine. The developed method allows the preparation of unsymmetrical disulfides bearing additional hydroxy, carboxy, amino, azido, biotin, or maleimide functionalities.

The synthesis of unsymmetrical disulfides is an important transformation in modern organic synthesis and medicinal chemistry.[1] The recent developments in disulfide bond formation have been reviewed.[2] Disulfides have also been used for the preparation of self-assembled monolayers (SAMs)[3] and monolayer-protected clusters (MPCs) with a number of versatile properties.[4]

Thioesters are readily available from alcohol, alkyl halide, or alkene derivatives,[5] and traditionally are converted into the corresponding thiols. Deprotection of the thiol group by removal of the acyl group can occur under basic, acidic, or neutral conditions. However, the formation of symmetrical disulfides, instead of the expected thiol, is observed very frequently when deprotection is performed under basic conditions, when open to the atmosphere or when solvent with dissolved oxygen from air is used.[6]

Thiols are relatively labile under ambient atmosphere and thus a transformation is highly desired in which protected thiols can be directly converted into disulfides, especially unsymmetrical examples. Convenient one-pot syntheses of symmetrical disulfides from thioacetates by nickel boride catalyzed methanolysis and disproportionation,[7] hydrolysis catalyzed by sodium azide[6b] or treatment with alkoxystannanes and ferric chloride[8] have been reported. Treatment of thiobenzoates with piperidine[9] or samarium diiodide[10] can also afford symmetrical disulfides. Much more interesting from the synthetic point of view is the direct conversion of thioesters into unsymmetrical disulfides. Cosstick and co-workers have presented the preparation of *S*-nucleosidyl *S*-aryl disulfides[11] from the corresponding *S*-nucleosidyl thiobenzoates.

We have previously demonstrated the preparation of functionalized unsymmetrical molecules such as dialkyl disulfides, alkyl-aryl disulfides,[12] 'bioresistant' disulfides,[13] unsymmetrical disulfides of L-cysteine and L-cystine,[14] and diaryl disulfides[15] 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,[16] and symmetrical[17] and unsymmetrical[18] trisulfides. In continuation of our interest in using disulfanyl derivatives **1** of phosphorodithioic acid for the preparation of functionalized unsymmetrical disulfides, herein we report an efficient and convenient synthesis of unsymmetrical disulfides directly from thioacetates (Table 1).

The idea is based on the chemoselective deprotection of thioacetates with sodium methoxide (method A, Table 1) or butylamine (method B, Table 1) in the presence of disulfanyl derivatives **1**. The generated thiolate anion reacts quickly with electrophilic disulfanyl derivative **1** to produce the corresponding functionalized unsymmetrical disulfide **3**. We have found that the use of a small excess of compound **1** (1.05 equiv) was required to avoid potential disulfide–thiol exchange and formation of symmetrical disulfides. This is important, especially in the case when the symmetrical product cannot be separated from the unsymmetrical derivative by column chromatography.

Under the optimized reaction conditions, the scope and generality of the disulfide formation were explored (Table 1).[19] In general, the yields of the unsymmetrical dialkyl disulfides **3** were

* Corresponding author. Tel.: +48 58 347 1851; fax: +48 58 347 2694.
E-mail address: dwitt@chem.pg.gda.pl (D. Witt).

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