A Novel and Efficient Synthesis of Unsymmetrical Disulfides

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Received 17 October 2006; revised 30 October 2006

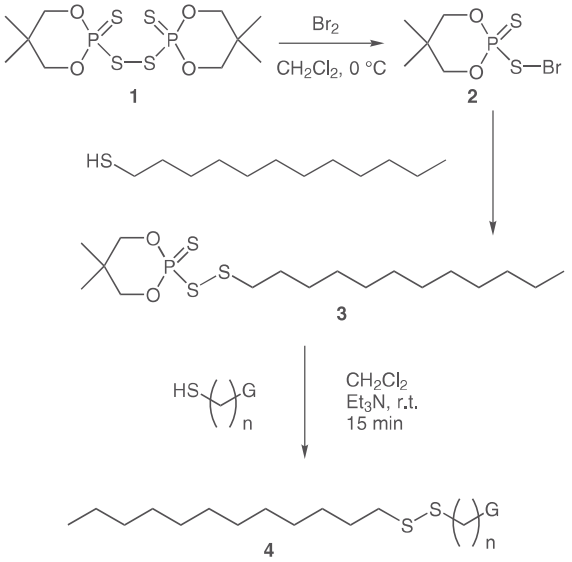
Abstract: Unsymmetrical disulfides have been prepared from the corresponding thiols and bis-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl)disulfide under mild conditions with good to excellent yields. The method can be applied to thiols bearing neutral, aromatic, basic or acidic functionalities with variable length of carbon chain.

Key words: unsymmetrical disulfides, alkanethiols, L-cysteine, thiophenol

Disulfides are important compounds for both chemical and biological processes,[1] and there are many biologically active peptides and peptide mimetics that possess unsymmetrical disulfide bonds.[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]

Perhaps the most common method for the preparation of disulfides is the oxidation of the appropriate thiols. The ease of oxidation usually decreases from aromatic thiols, through primary and secondary, to tertiary. Mixed disulfides may be prepared using this method, although a statistical ratio of disulfide products is expected. However, when sufficient structural differentiation between the two thiols is present, for example the oxidation of benzylthiol in the presence of *tert*-butylthiol,[5] then the unsymmetrical disulfide can become the major product. Preparative methods that are efficient for the preparation of symmetrical disulfides are very often ineffective for the preparation of unsymmetrical disulfides. The most widely used method for obtaining unsymmetrical disulfides involves the thioalkylation of a thiol by derivatives of *N*-sulfenylphthalimide,[6] *N*-sulfenamides[7] (from diethyl azodicarboxylate; DEAD), sulfenyl chlorides,[8] Bunte salts[9] and 2-pyridyldisulfide[10] (obtained from Aldrithiol). Thiolysis is favored for the synthesis of unsymmetrical disulfides by the above methods, although yields may be compromised by the long reaction times required and by rapid thiol–disulfide exchange reactions.

Herein, we report a new and versatile synthesis of unsymmetrical disulfides based on the stable and readily available bis(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl)disulfide (**1**).[11] The procedure developed is rapid (15 minutes) and proceeds under mild conditions to give excellent yields (90–100%). Unsymmetrical disulfides can be prepared from thiols bearing neutral, aromatic, basic or acidic functionalities with variable lengths of the carbon chain. The synthetic strategy is presented in Scheme 1.



Scheme 1 The synthesis of unsymmetrical disulfides **4**. The structure of group G is presented in Table 1.

The disulfide reagent **1** was treated with bromine at 0 °C to afford (5,5-dimethyl-2-thiono-1,3,2-dioxophosphorinanyl)sulfenyl bromide (**2**),[12] which was reacted, without isolation, with 1-dodecanethiol. The 5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl-2-disulfanyldodecane (**3**) was isolated in quantitative yield. Compound **3** was then treated with a variety of thiols in order to examine the scope and limitations of the method. The results are summarized in Table 1.

We selected thiols bearing hydroxyl (run 1), amino (run 2), *tert*-butoxycarbonylamino (run 3), *N*-hydroxysuccinoimidyl ester (run 4), carboxyl (with different carbon chain lengths; run 5 and 6), aromatic groups (runs 9–12), L-cysteine ethyl ester (run 7) and *N*-acetyl-L-cysteine (run 8). All the above compounds afforded, after purification, unsymmetrical disulfides **4** with excellent yield. We observed that, very often, crude products were good enough for further synthetic elaboration. The purity was estimated by ^{1}H NMR spectroscopy to be about 90% (the major contamination was from dithiophosphoric acid). As can be seen in Table 1, the presence of nucleophilic and electrophilic functionalities did not perturb the reaction. These results make this procedure currently one of the most ver-

SYNTHESIS 2007, No. 3, pp 0363–0366
Advanced online publication: 08.01.2007
DOI: 10.1055/s-2007-965873; Art ID: P12206SS