Functionalization of Cysteine Derivatives by Unsymmetrical Disulfide Bond Formation

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Abstract: We have developed a convenient method for the synthesis of unsymmetrical disulfides of L-cysteine under mild conditions in good to excellent yields. The described method is based on the straightforward preparation of 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-sulfenyl bromide from readily available bis(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) disulfide. The unsymmetrical disulfides can be obtained for L-cysteine derivatives and thiols bearing neutral, basic, or acidic functionalities.

Key words: unsymmetrical disulfides, L-cystine, L-cysteine, sulfenyl bromide, thiols

The disulfide bond plays an important role in the construction of secondary and tertiary polypeptide and protein structures. Modern methods of forming unsymmetrical disulfide bonds are required for the synthesis of many biologically active peptides, peptide mimetics,[1] prodrugs, and antibiotics.[2] A range of sulfur-protecting groups and strategies for their removal are available that are sufficiently selective to allow the synthesis of compounds with four or more disulfide bonds. Nevertheless, the problems associated with the use and manipulation of these protective groups continues to drive the search for alternative sulfur-protection strategies and new, more versatile methods for the formation of unsymmetrical disulfide bonds. Although many different methods exist for the preparation of unsymmetrical disulfides, the most prevalent approach involves substitution of a sulfenyl derivative with a thiol or its derivative. The most commonly utilized sulfenyl derivatives to date include: sulfenyl chlorides,[3] *S*-alkyl thiosulfates and *S*-aryl thiosulfates (Bunte salts),[4] *S*-(alkylsulfanyl)isothioureas,[5] benzothiazol-2-yl disulfides,[6] benzotriazolyl sulfides,[7] dithioperoxyesters,[8] (alkylsulfanyl)dialkylsulfonium salts,[9] 2-pyridyl disulfides and derivatives,[10] *N*-alkyltetrazolyl disulfides,[11] sulfenamides,[12] sulfenyldimesylamines,[13] sulfenyl thiocyanates,[14] 4-nitroarenesulfenanilides,[15] thiolsulfinates and thiolsulfonates,[16] sulfanylsulfinamidines,[17] thionitrites,[18] sulfenyl thiocarbonates,[19] thioimides,[20] and thiophosphonium salts.[21] Other practical procedures involve: reaction of a thiol with a sulfinylbenzimidazole,[22] rhodium-catalyzed disulfide exchange,[23] an electrochemical method,[24] and the use of diethyl azodicarboxylate[25] or solid support[26] in a sequential coupling of two different thiol groups.

Recently, we discovered that readily available *S*-thioacyl dithiophosphates are excellent thioacylating agents. These mixed anhydrides chemoselectively thioacylate nitrogen or sulfur nucleophiles in the presence of hydroxy groups. This property allowed us to obtain hydroxy thioamides, hydroxy dithioesters, and thiohydroxamic acids, from substrates with unprotected oxygen atoms.[27] We were encouraged by these results, so we designed a synthetic strategy to prepare unsymmetrical disulfides based on mixed anhydrides of dithiophosphoric acids. We have previously demonstrated the application of organophosphorus sulfenyl bromides (mixed anhydrides of dithiophosphoric acid and hydrobromic acid) for the preparation of functionalized unsymmetrical molecules, such as dialkyl disulfides, alkyl aryl disulfides,[28] and 'bioresistant' disulfides.[29] The excellent results encouraged us to extend this strategy to the preparation of unsymmetrical disulfides of L-cysteine and L-cystine based on organophosphorus sulfenyl bromides as activating agents for unsymmetrical disulfide bond formation.

The stable and readily available bis(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) disulfide (**1**)[30] was treated with bromine at –30 °C to afford quantitatively 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-sulfenyl bromide (**2**).[31] The organophosphorus sulfenyl bromide **2** was unstable at room temperature and afforded mainly 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl bromide upon isolation.

When sulfenyl bromide **2** was treated at –30 °C without isolation with octadecane-1-thiol, 11-sulfanylundecanoic acid, 2,5-dioxopyrrolidin-1-yl 11-sulfanylundecanoate, 11-azidoundecane-1-thiol, 11-(*tert*-butoxycarbonylamino)undecane-1-thiol, *N*-(*tert*-butoxycarbonyl)-L-cysteine ethyl ester, or 2-sulfanylethanol then the 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yldisulfanyl derivatives **3a–g** were isolated in excellent yield (Table 1).

The reaction of sulfenyl bromide **2** with octadecane-1-thiol afforded disulfanyl derivative **3a** in excellent yield; HBr was formed as a side product. However, in the presence of triethylamine, the same reaction gave dioctadecyl disulfide (symmetrical disulfide) as the major product (98%), and the formation of **3a** was not observed. Moreover, the reaction of disulfanyl derivative **3a** with *N*-acetylcysteine did not occur in the absence of triethylamine, and after several hours, only traces of unsymmetrical di-

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